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PART ONE

SOME STEREOCHEMICAL RELATIONSHIPS AMONG SULFOXIDES, SULFILIMINES AND SULFOXIMINES

PART TWO

THE STEREOCHEMICAL COURSE OF THE REACTION OF ALKYL SULFONATE ESTERS WITH ARYL GRIGNARD REAGENTS

By

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B. S., Saint Peter's College, 1964

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August 21, 1968
Date

ABSTRACT

I. Optically active sulfoxides of known configuration were converted to sulfoximines under the conditions of the Kwart-Kahn reaction: methanol heated to reflux, aryl sulfonyl azide, copper and sulfoxide. The reaction produced optically active sulfoximines, whose absolute configurations were established by relating them to optically active sulfilimines of known configuration. The ORD, CD, and uv spectra of the optically active sulfoximines were taken. The levorotatory sulfoximines of the (R) configuration show a (-) Cotton effect at about 230 mμ. The work establishes some useful correlations among optically active sulfoxides, sulfilimines and sulfoximines.

II. The stereochemical course of the reaction of an alkyl sulfonate ester with an aryl Grignard reagent was established. Isotopic ^{18}O-(-)-menthyl p-toluenesulfonate was prepared by the oxidation of the corresponding sulfinate with ^{18}O-potassium permanganate. The sulfonate ester, when treated with an aryl Grignard reagent, produced an optically active sulfone, whose configuration is known. It was found that ^{18}O-(-)-menthyl α-toluenesulfonate ester of the (R) configuration with p-tolylmagnesium bromide produced levorotatory ^{18}O-benzyl p-tolyl sulfone of the (S) configuration. Therefore, the Grignard reaction proceeded with inversion of configuration.

ACKNOWLEDGMENT

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Michael A. Sabol
MICHAEL A. SABOL

THIS THESIS IS DEDICATED TO MY PARENTS

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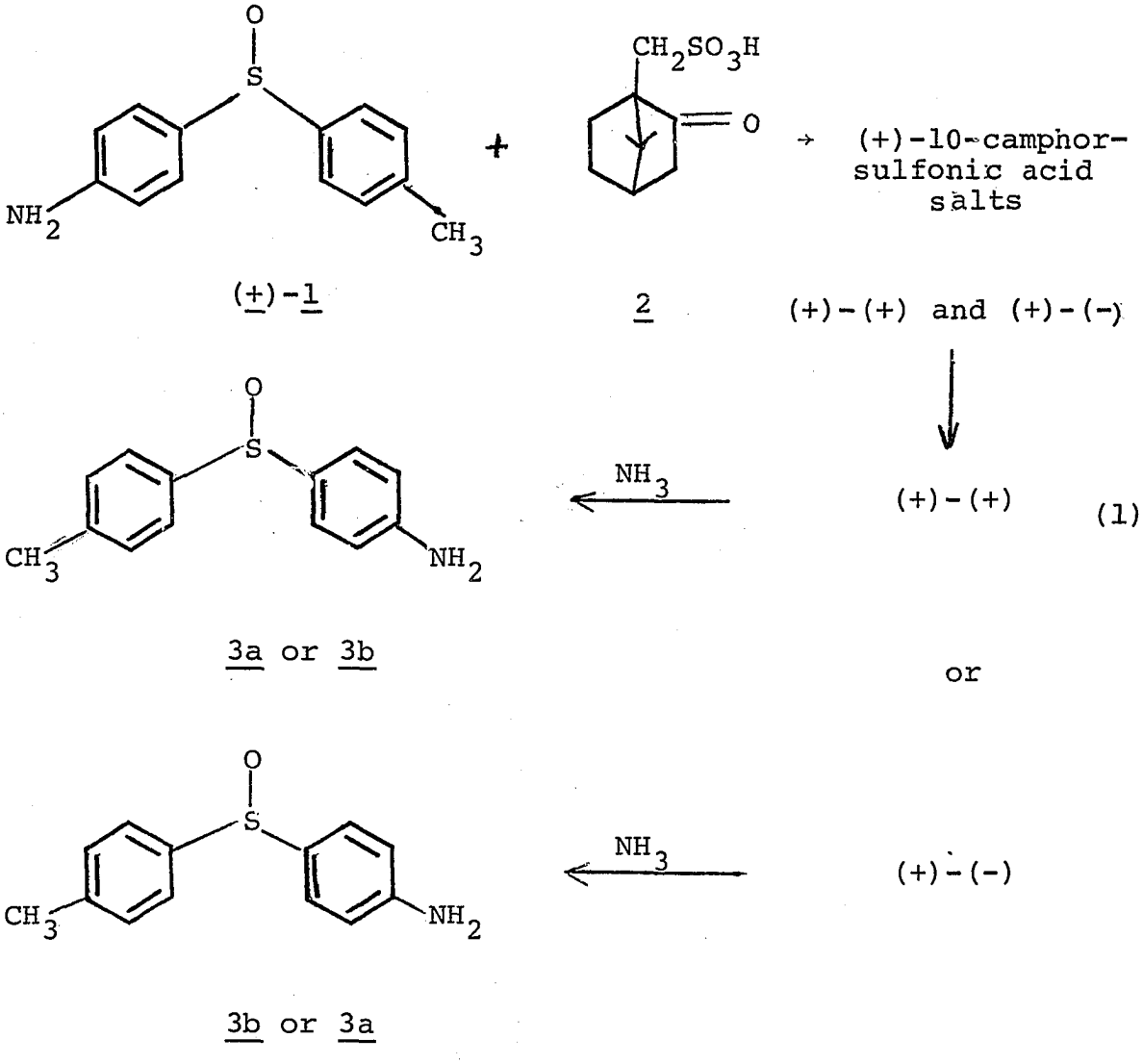
PART I

INTRODUCTION

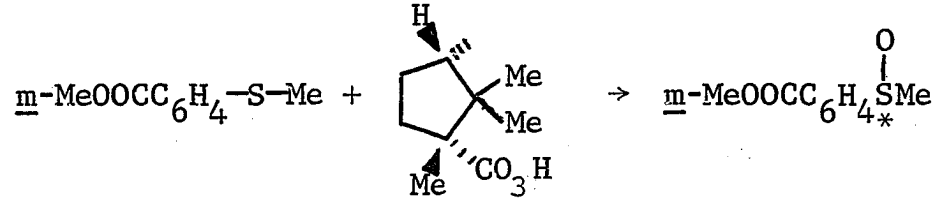
Stereoisomerism has been found to be an important tool for investigating the course of an organic reaction. Knowledge of the intermediate of the reaction under consideration may usually be deduced from the optical properties of the products obtained. The formation of a symmetrical intermediate in a reaction involving optically active compounds as starting materials results in the isolation of optically inactive products. Recovery of optically active products indicates a stereospecific reaction pathway.

The asymmetry at the sulfur atom in sulfoxides, sulfilimines, and sulfoximines has been established by resolution of members of these classes of compounds. Harrison, Kenyon and Phillips[1] reported the first isolation of a sulfoxide in an optically active form. (+)-4'-Amino-4-methyldiphenyl sulfoxide (1) was treated (eq 1) with (+)-10-camphorsulfonic acid (2) to yield diastereomeric salts which were separated by crystallization. After decomposition of the salts, a dextrorotatory sulfoxide (3a), $[\alpha]_{546}$ +123° (chloroform), and a levorotatory sulfoxide (3b), $[\alpha]_{546}$ -122° (ethanol), were obtained.



Other more widely applicable syntheses of optically active sulfoxides have since been reported. Among these are the oxidation of an optically inactive sulfide with an optically active acid (eq 2);[2,3] the oxidation of a sulfide containing an optically active group with an inactive acid (eq 3);[4] and conversion of optically active sulfinate esters to optically active sulfoxides by means of a Grignard reagent

(eq 4).[5,6] Good yields of sulfoxides of high optical purity were produced by the last method (eq 4).



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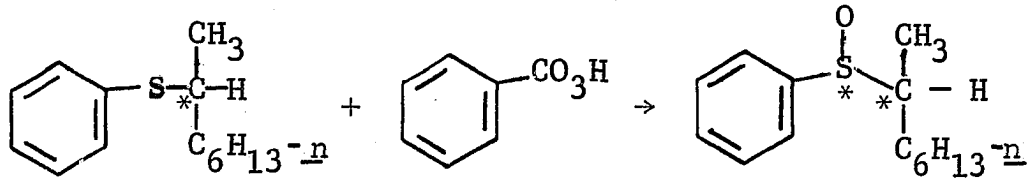

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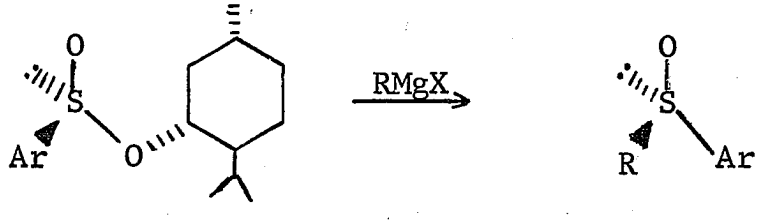
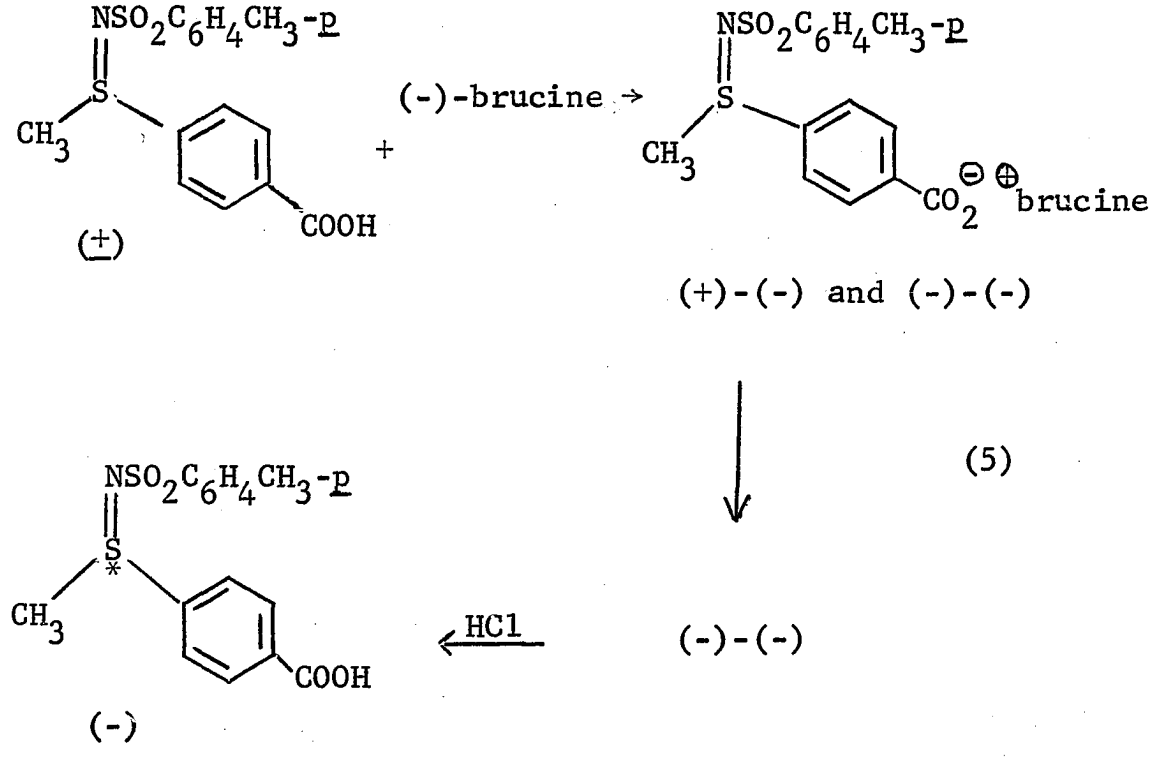


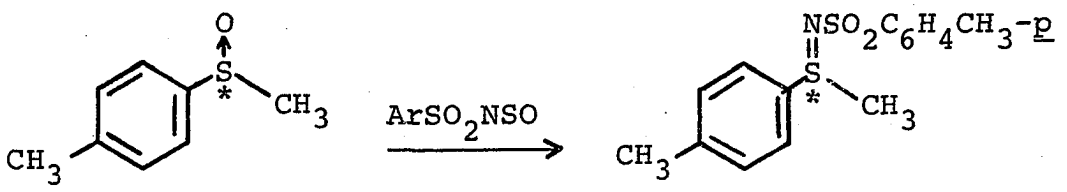
(4)

Clark, Kenyon and Phillips[7] succeeded in isolating an optically active sulfilimine in 1927. (±)-S-Methyl-S-(m-carboxyphenyl)-N-p-toluenesulfonylsulfilimine was prepared by the condensation of chloramine T with m-carboxyphenyl methyl sulfide. The diastereomeric brucine salts of the resulting sulfilimines were prepared and separated by crystallization. The less soluble (-)-brucine-(-)-S-methyl-S-(m-

carboxyphenyl)-N-p-toluenesulfonylsulfilimine was decomposed with hydrochloric acid to yield the levorotatory sulfilimine, $[\alpha]_{5461}$ -388° (ethanol).



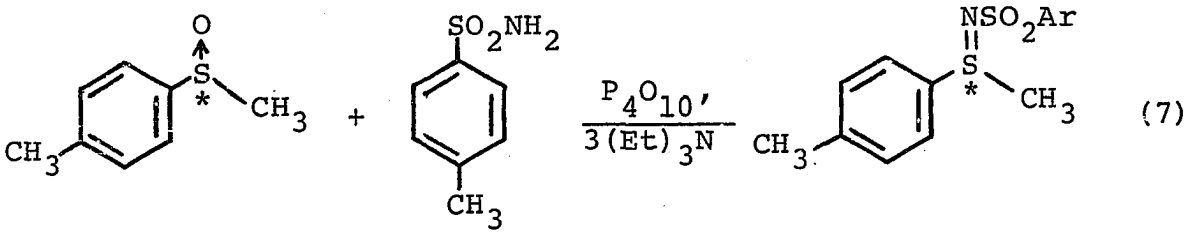
Schulz and Kresze[8] reported the preparation of sulfilimines by the reaction of a sulfoxide with N-sulfinyl-p-toluenesulfonamide. Later Day and Cram[9] showed that this reaction was stereospecific and therefore could be used to prepare optically active sulfilimines (eq 6).



(6)

Ar = p-$CH_3C_6H_4$-

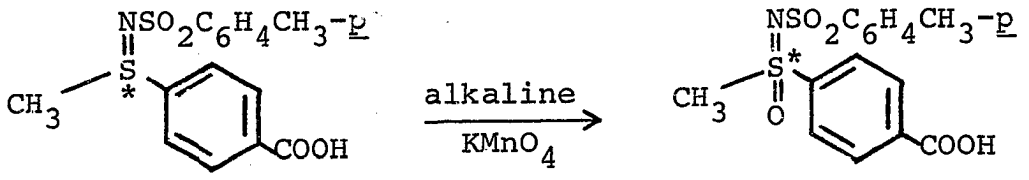
Day and Cram[9] also reported the preparation of optically active sulfilimines from the reaction of optically active sulfoxides with p-toluenesulfonamide in the presence of a dehydrating agent (eq 7).



(7)

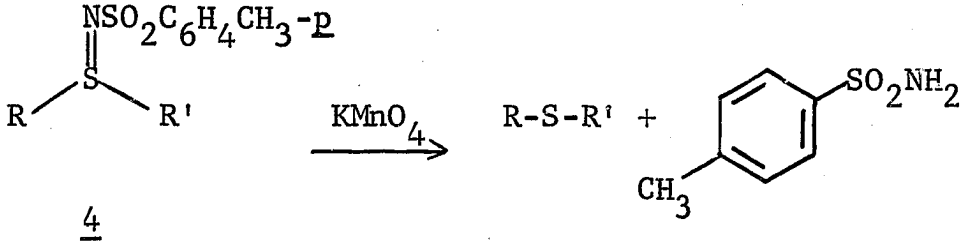
Ar = p-$CH_3C_6H_4$

The first optically active sulfoximines, which owed all of their optical activity to the sulfur atom as the asymmetric center, were synthesized by Kresze and Wustrow.[10] This was accomplished by oxidizing an optically active sulfilimine with alkaline potassium permanganate (eq 8).



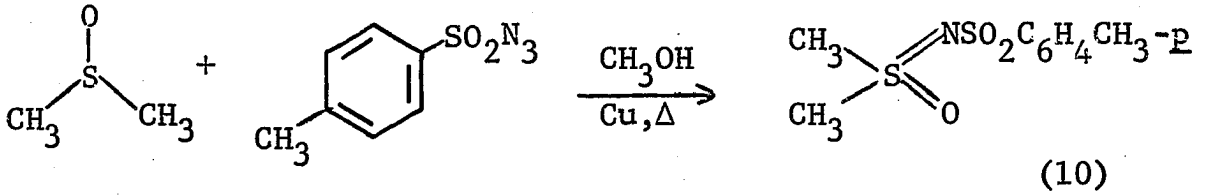
(8)

It is noteworthy that this oxidation in the large majority of cases proceeds with low yields.[11] The route to sulfoximines by oxidation is not an attractive synthesis since the success of the oxidation depends upon the resistance of the -S=N- bond of the sulfilimine toward cleavage. Thus oxidation of 4 (R=Me, R'=CH_2CH_2Cl or Ch_2CH_2OH)[12] with hydroxide or acetic acid results in the isolation of p-toluenesulfonamide (5) (eq 9).



4 (9)

Sulfoximines have recently been prepared by Kwart and Kahn[13] from sulfoxides. Dimethyl sulfoxide was treated with p-toluenesulfonyl azide to yield S,S-dimethyl-N-p-toluenesulfonylsulfoximine (eq 10). Since the reaction was carried out with inactive starting material, no knowledge was obtained concerning the stereochemical course of the reaction.



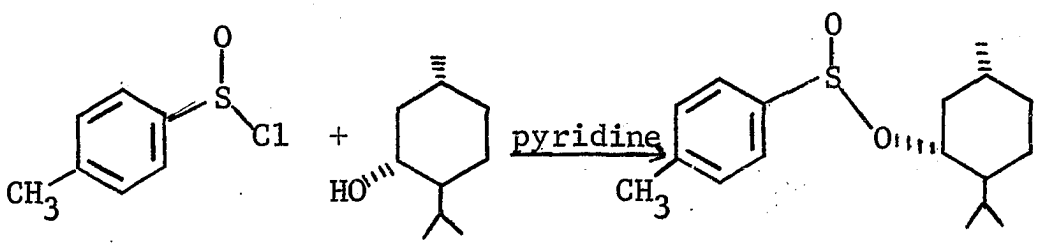
(10)

In view of the fact that the applicability of the oxidation of the optically active sulfilimine (eq 9) was

limited by the tendency of the -S=N- bond of the sulfilimine toward cleavage, a more convenient route to optically active sulfoximines was sought. This part of the thesis deals with the successful attempt to prepare optically active sulfoximines from optically active sulfoxides using the Kwart-Kahn reaction (eq 10). The work also establishes the absolute configuration of the resulting sulfoximines, the stereochemical course of the reaction, and some useful correlations among sulfoxides, sulfilimines, and sulfoximines.

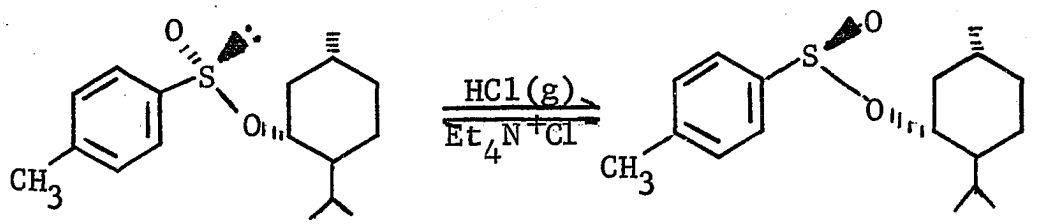
RESULTS AND DISCUSSION

Optically active sulfinate esters, precursors to optically active sulfoxides, can be synthesized by the reaction of racemic sulfinyl chlorides with (-)-menthol[14-16] (eq 1). The less soluble of the two diastereomers formed precipitates out of the ether-pyridine reaction mixture. Hydrogen chloride gas and tetraethylammonium chloride are added to the reaction mixture to equilibrate the two diastereomers (eq 2). By repeatedly reestablishing the equilibrium in the mother liquid, a very good yield (70-90%) of the less soluble isomer can be realized. The reaction (eq 1) and the epimerization (eq 2) are shown for (-)-menthyl p-toluenesulfinate.



(1)

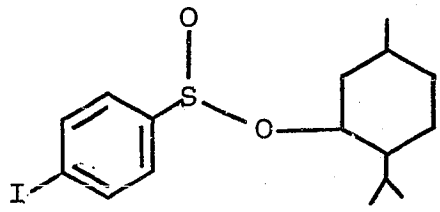
(+)-(-)-1 and (-)-(-)-1



(2)

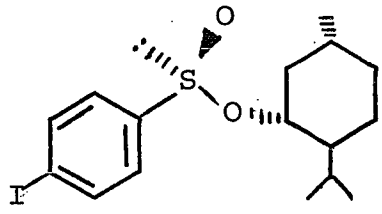
(+)-(-)-1 (-)-(-)-1

The assignment of the absolute configurations of (+)-(-)-1 and (-)-(-)-1 was accomplished in the following manner. The absolute configuration of a (-)-menthyl p-iodobenzenesulfinate diastereomer (2) was established by X-ray methods.[17]

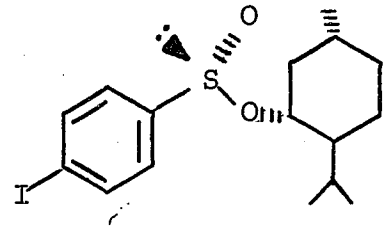


2

The absolute configuration around an atom can be determined by X-ray only if an internal standard atom of known configuration is present.[18] In the present case, since the absolute configuration of the (-)-menthol group is known, the absolute configuration of the sulfur atom in structure (2) can be ascertained. The absolute configuration around the sulfur atom in the levorotatory diastereomer was found to be (S).



(-)-(S)-2

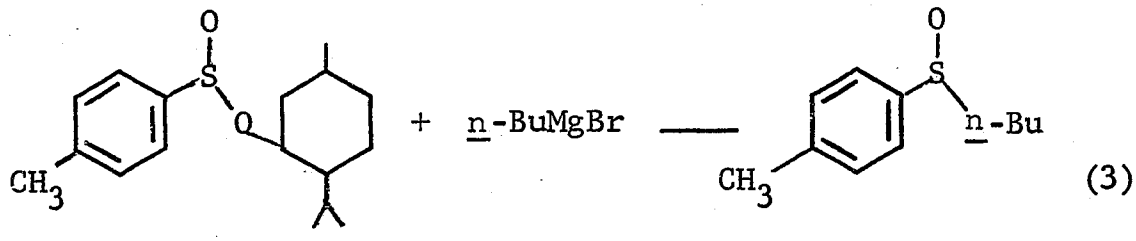


(+)-(R)-2

Mislow and co-workers[19] correlated the absolute configuration of the (-)-menthyl p-toluenesulfinates (1) with (-)-menthyl (-)-p-iodobenzenesulfinate (-)-(S)-2 by carrying out the following experiments.

The diastereomeric mixture (2) of (-)-menthyl p-iodobenzenesulfinates ((-)-2 and (+)-2) obtained by the reaction of racemic p-iodobenzenesulfinyl chloride with (-)-menthol had $[\alpha]_D$ -20.9°. The percentage of each diastereomer present was calculated from the reported[14] rotations of the pure diastereomeric components, $[\alpha]_D$ +22.7° and -145.8°. Mixture (2) was found to contain 74.1% of the diastereomer (+)-2. Under the non-equilibrating conditions of the experiment (+)-2 is the kinetically controlled major product.

The (-)-menthyl p-toluenesulfinate diastereomers (+)-1 and (-)-1 were formed under the same reaction conditions as above. The resulting mixture (1) had $[\alpha]_D$ -38.5°. The rotation of only one of the pure (-)-menthyl p-toluenesulfinates (-)-1 was known ($[\alpha]_D$ -206°); the rotation of the other diastereomer was determined in the following way.



1 3 (3)

Mixture (1) was treated with n-butyl magnesium bromide to form a mixture (3) of n-butyl sulfoxides which had $[\alpha]_D$ -51°.

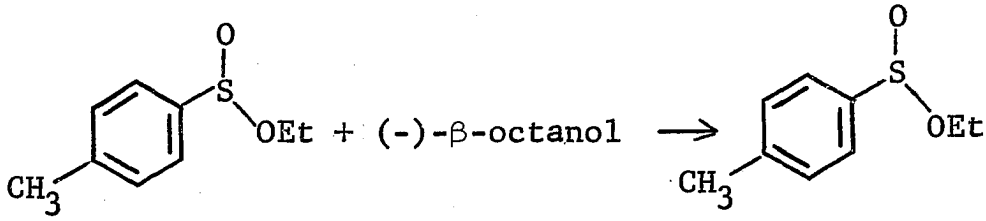
Pure n-butyl p-tolyl sulfoxide (+)-3, obtained from diastereomerically pure (-)-1, had $[\alpha]_D$ +187°. Therefore the mixture (3) of sulfoxides contained 63.6% of the (-) enantiomer ((-)-3). It was assumed that the ratio of enantiomers in mixture 3 reflected the ratio of diastereomers in mixture 1. Since the rotation of mixture 1 ($[\alpha]_D$ -38.5°), the rotation of (-)-1 ($[\alpha]_D$ -206°), and the ratio of diastereomers in mixture 1 (63.6% : 36.4%) were all known, the rotation of the remaining diastereomer (+)-1 could be calculated to be $[\alpha]_D$ +57.4°. It followed that (-)-menthyl (+)-p-toluenesulfinate (+)-1 is the isomer present in 63.6% yield and is therefore the kinetically controlled product.

To insure that the above assumption (i.e., that the ratio of enantiomers in sulfoxide mixture 3 represented the ratio of diastereomers in sulfinate ester mixture 1) was valid, Mislow altered the ratio of diastereomers in mixture 1 by adding pure (-)-(-)-1 to mixture 1 until mixture 1 contained 66.9% of (-)-(-)-1. When this new mixture was treated with n-butyl Grignard reagent, the ratio of n-butyl p-tolyl sulfoxides produced contained 66.9% of the (+) enantiomer. From this experiment it appears that the assumption is valid.

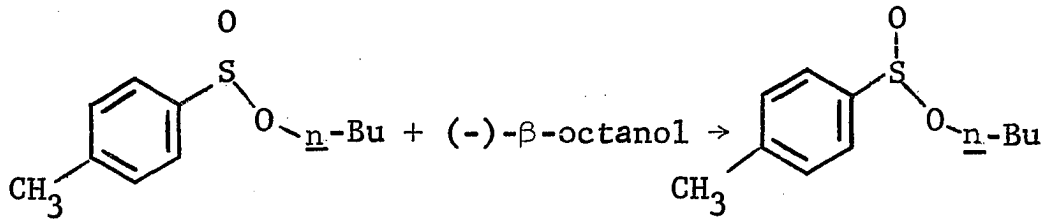
It is reasonable to conclude from the above arguments that dextrorotatory (-)-menthyl p-iodobenzenesulfinate ((+)-2) and dextrorotatory (-)-menthyl p-toluenesulfinate ((+)-1) have the same configuration around sulfur since both were the kinetically controlled major products in the reactions of their respective sulfinyl chlorides with (-)-menthol.

Therefore, the configuration at sulfur in the dextrorotatory (-)-menthyl p-toluenesulfinate ((+)-1) is (S).

The preparation of sulfoxides from arylsulfinate esters involves a nucleophilic attack on the sulfur by the Grignard reagent. Nucleophilic attack on a trigonal sulfur atom has been shown to proceed by inversion of configuration in three cases. The first example[20] involves the alcoholysis (eq 6) of (-)-ethyl p-toluenesulfinate (4).



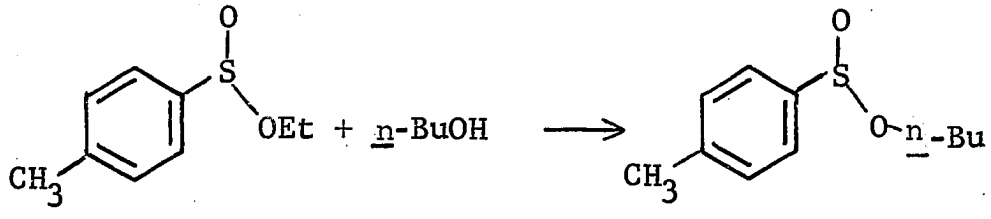
4 (2 moles) (1 mole) (-)-4 (4)



5 (2 moles) (1 mole) (-)-5 (5)

Excess ethyl p-toluenesulfinate (4) and excess n-butyl p-toluenesulfinate (5) were each treated with (-)-β-octanol (eq 4 and eq 5). It was concluded that the (-)-4 and (-)-5 produced had the same configuration around sulfur since the small difference of the alkyl group in the ester

would not be expected to effect a preference for different enantiomers. If (-)-β-octanol reacted faster with the (R) isomer in eq 4, it would be expected to react faster with the (R) isomer in eq 5.

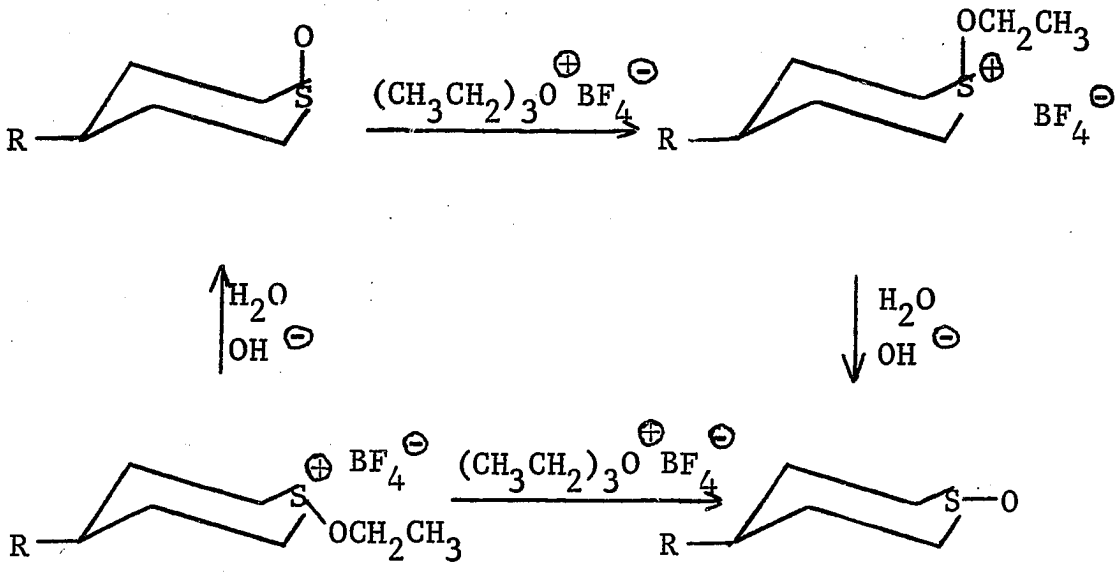


(6)

(-)-4 (+)-5

When (-)-4 was treated with n-butyl alcohol, dextrorotatory n-butyl p-toluenesulfinate ((+)-5) resulted. Since (-)-4 and (-)-5 had been shown to have the same configuration (eq 4 and eq 5), the production of (+)-5 from (-)-4 in eq 6 indicated that the alcoholysis reaction proceeded with inversion.

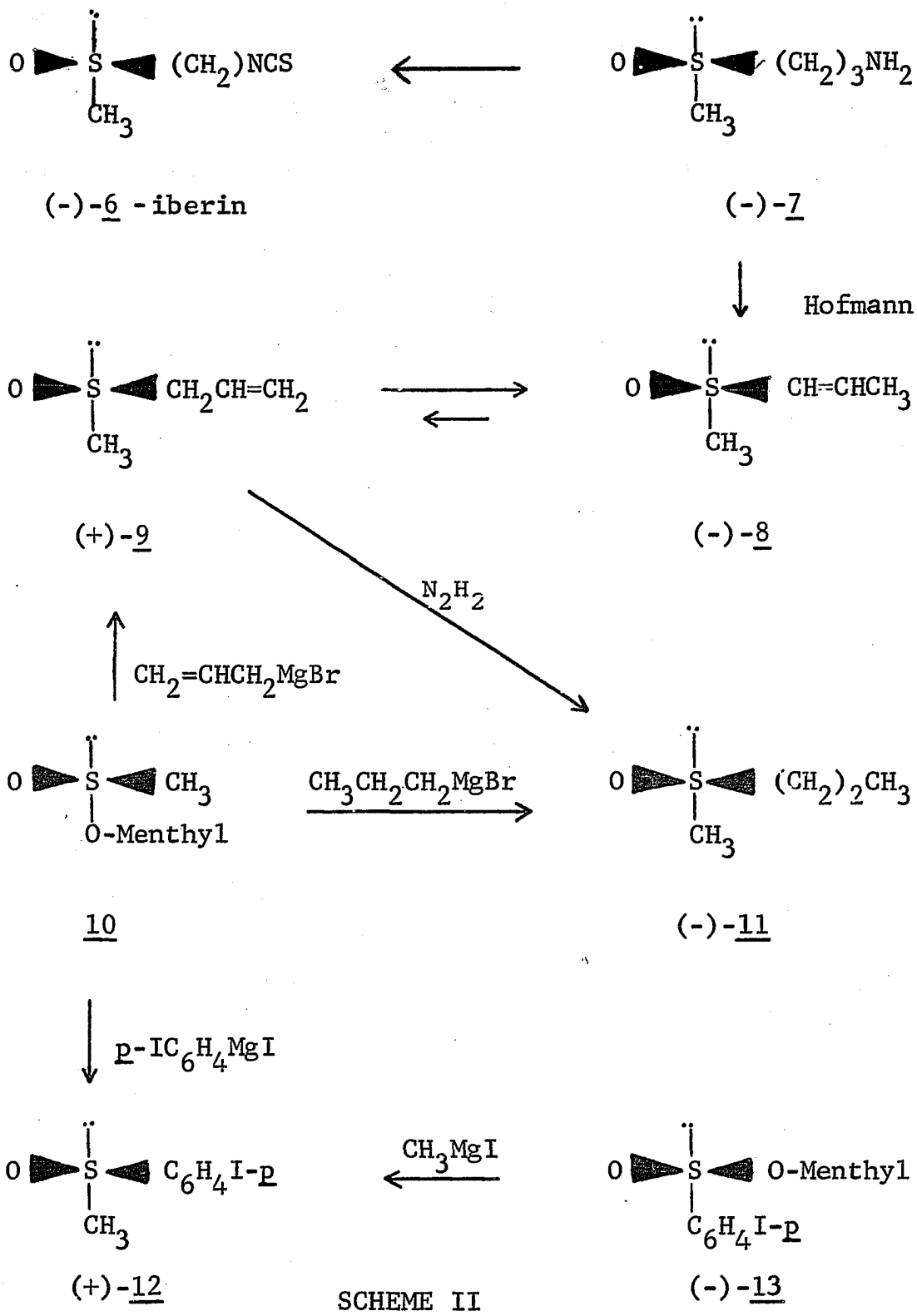
The second case[21] of an inversion reaction concerning nucleophilic attack on trigonal sulfur involves the inversion of the sulfoxide configuration. cis- and trans-4-(p-Chlorophenyl)-thian-1-oxides were interconverted with triethyloxonium fluoroborate as illustrated in Scheme I.



R = p-ClC$_6$H$_4$-

SCHEME I

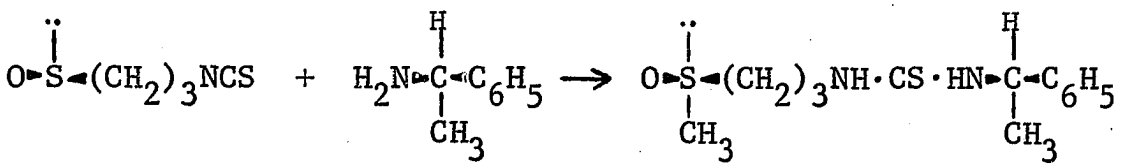
Finally, the most convincing arguments in favor of inversion of configuration in the reaction of sulfinate esters with Grignard reagents was presented by Mislow and co-workers.[22] (-)-Menthyl (-)-p-iodosulfinate (13) and (-)-iberin (6), two compounds whose absolute configurations had been determined by X-ray methods, were related by a series of reactions. The reaction sequence is presented below.



SCHEME II

The absolute configuration of (-)-iberin (6) was established[23] through conversion of 6 into its thiourea

derivative (15) by means of reaction with (+)-α-methylbenzylamine (14) (eq 7). The X-ray analysis of the thiourea derivative indicated that the absolute configuration around the sulfur atom was (R).



(7)

6 (+)-(R)-14 15

The absolute configuration around the sulfur atom in (-)-13 had previously been shown[17] by X-ray analysis to be (S).

The absolute configuration of (-)-7 was established as (R) by conversion of this compound to (-)-iberin (6). Under the conditions of the Hofmann elimination (-)-7 yielded a product ($[\alpha]_D$ -142° (ethanol)) which was found to contain 20% of (+)-9 and 80% of (-)-8 by nmr. It is not expected that the stereochemistry of the sulfur atom would be affected during this Hofmann elimination so the (R) configuration was established for both (+)-9 and (-)-8.

The diastereomeric purity of a mixture of (-)-menthyl methanesulfinates, (10) presumably enriched in the (R) epimer,[24] was determined by conversion to sulfoxides. It had been previously shown[19] that in the reaction of sulfinate esters with Grignard reagents, the ratio of enantiomers in the product sulfoxides reflected the ratio of diastereomers in the starting

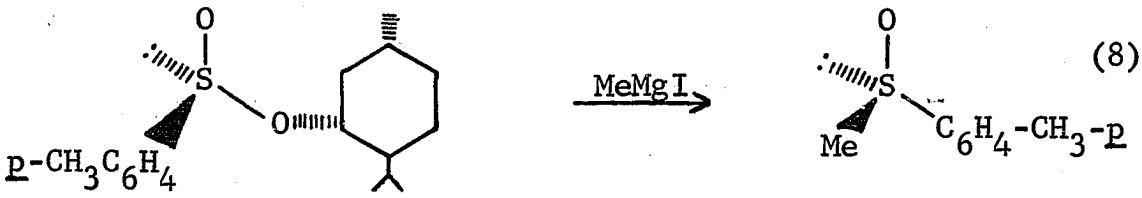
ester. Using this technique, 10 was found to be 32.4% diastereomerically pure. Treatment of 10 with n-propylmagnesium bromide yielded (-)-methyl n-propyl sulfoxide (-)-11, $[\alpha]_D$ -42° (ethanol). Also, treatment of 10 with allylmagnesium bromide gave (+)-9, $[\alpha]_D$ +4.9° (ethanol). Reduction of (+)-9 with diimide yielded (-)-11, $[\alpha]_D$ -35° (ethanol). Since the configuration of (+)-9 had been established as (R) (above), the (R) configuration was assigned to (-)-11.

A similar diastereomeric mixture of 10, 29% diastereomerically pure, when reacted with p-iodophenylmagnesium iodide yielded (+)-methyl p-iodophenyl sulfoxide (12). (+)-12 must have the same configuration as (-)-11 and (+)-9 since all arise from the same precursor. Thus (+)-12 has the (R) configuration. The only assumption made here is that the three Grignard reactions leading to 9, 11, and 12 all have the same stereochemical paths.

The reaction of methylmagnesium iodide with diastereomerically pure (-)-menthyl (-)-p-iodobenzenesulfinate ((-)-13) yielded (+)-12, $[\alpha]_D$ +99° (ethanol). Since the absolute configuration of (-)-13 has been shown[17] by X-ray to be (S) and the absolute configuration of (+)-12 has been shown by the above chemical transformations to be (R), the Grignard reaction converting (-)-(S)-13 to (+)-(R)-12 can be said to proceed with inversion.

Since the absolute configuration of the arylsulfinate esters has been established[17,19] and, since the Grignard reaction has been shown to proceed with inversion,[20,21,22]

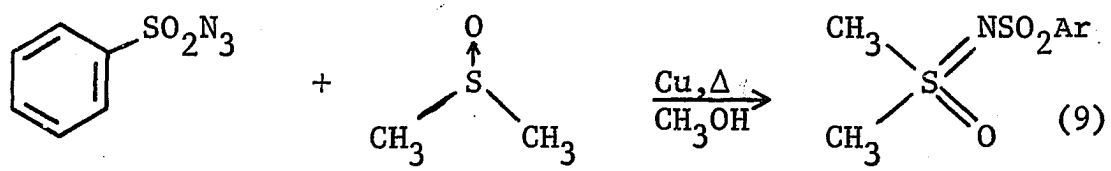
the absolute configuration of the resulting sulfoxides can be assigned. It has been found that when arylsulfinate esters of the (S) configuration are treated with alkyl Grignard reagents, sulfoxides of the (R) configuration are formed (eq 8).



(8)

(-)-(S) (+)-(R)

Kwart and Kahn[13] reported the formation of S, S-dimethyl-N-p-toluenesulfonylsulfoximine (16) by the reaction of 17 with benzenesulfonyl azide (18) in the presence of copper (eq 9).

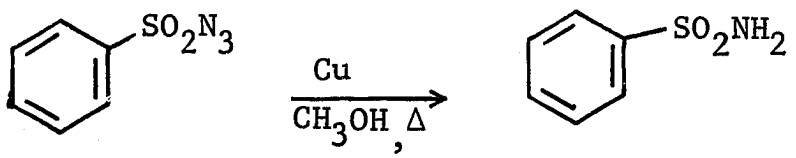


(9)

18 17 16

The following data were found to be true about the decomposition of the azide (18).

a) In the absence of dimethyl sulfoxide the reaction of 18 resulted in an 80% yield of benzenesulfonamide (19) (eq 10).



(10)

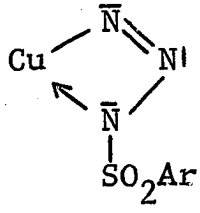
18 19

b) The reaction of 18 is much slower in the absence of copper (eq 10).

c) In the absence of copper the reaction (eq 9) proceeded at a much slower rate than in the presence of copper.

d) In the absence of dimethyl sulfoxide the reaction of 18 leading to benzenesulfonamide (eq 10) is slower than the reaction leading to 16 (eq 9) with dimethyl sulfoxide present.

It was interpreted[13] from fact b that copper was acting as a catalyst in the reaction, probably by formation of a copper-azide complex (20) which caused a reduction of the activation energy for nitrogen evolution. The loss of nitrogen from (20) was thought[13] to result in the formation (eq 11) of a copper-nitrene complex (21) which reacted with solvent to form the amide (19).



$$\longrightarrow \quad N_2 + [Cu \Longleftarrow NSO_2Ar] \qquad (11)$$

20 21

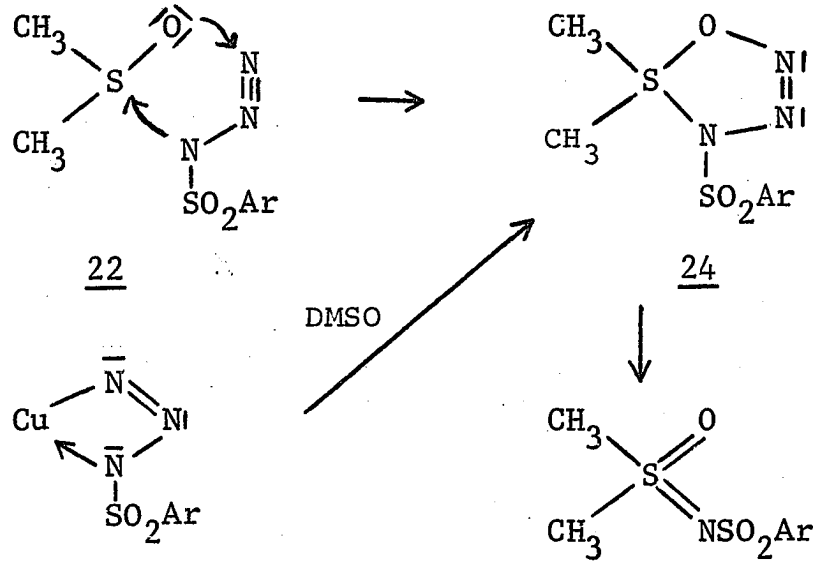
$$21 \xrightarrow{CH_3OH} Cu^\circ + ArSO_2NH_2 + H_2C{=}O$$

19

Complexes similar to 21 have been reported[25] in the copper catalyzed decompositions of diazoalkanes.

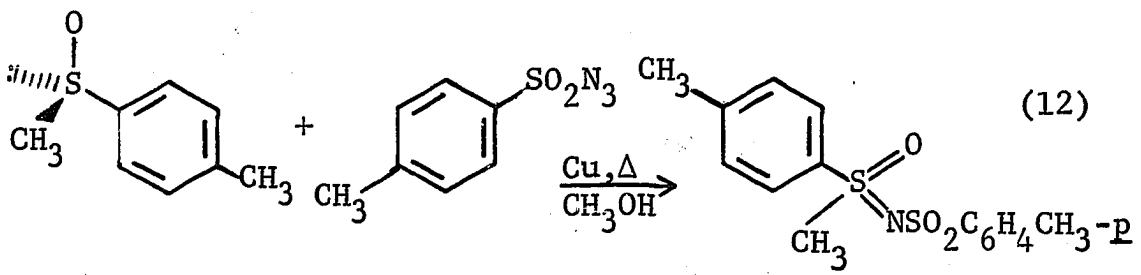
Statement c supported the idea of catalysis by copper.

Dimethyl sulfoxide was thought to participate in the initial steps of the decomposition (eq 9) because of the experimental result stated in d. It was not known whether this participation involved a 1,3-dipolar addition to the azide as represented by 22, or interaction of dimethyl sulfoxide with the copper azide complex (23). Either possibility can lead to the same intermediate (24).



In order to determine whether the reaction converting sulfoxides to sulfoximines (eq 9) proceeded by a path

capable of preserving stereochemistry, it was decided to carry out the reaction using optically active starting materials. Optically active (+)-(R)-methyl p-tolyl sulfoxide (25) was submitted[26] to the conditions of the Kwart-Kahn reaction and was found to yield an optically active sulfoximine (26) (eq 12).



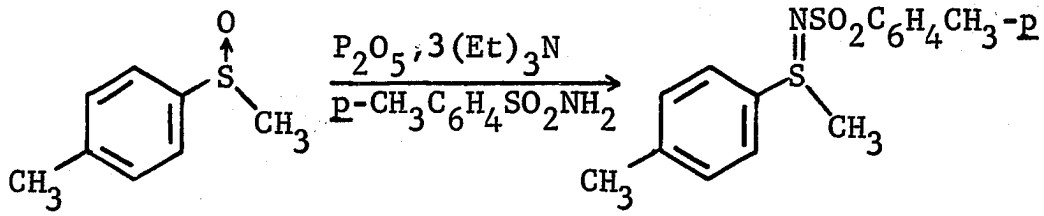
(12)

25 26

optically active

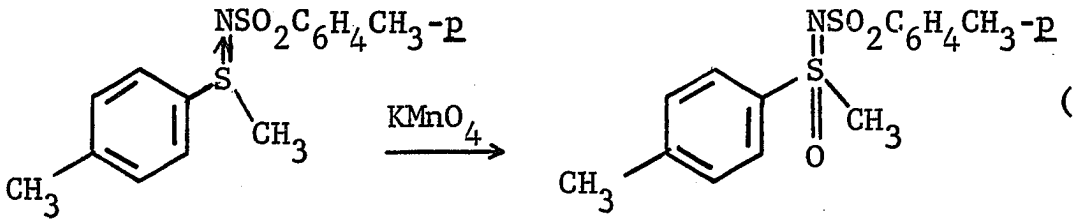
The absolute configuration of (26) was determined[26] by synthesizing the same sulfoximine using only reactions whose stereochemical paths have been elucidated. The reaction sequence that was employed is shown in Scheme III.

Day and Cram[9] determined the stereochemical course of eq 13. Optically pure[19] (+)-27 was converted to (-)-28 by reaction with phosphorus pentoxide and p-toluenesulfonamide. The sulfilimine (-)-28 was then converted back to the sulfoxide (+)-27 by means of potassium hydroxide (eq 15). The fact that the (+)-27 recovered from this reaction (eq 15) was found to be 94% optically pure indicated that compound (-)-28 obtained from eq 13 was at least 94% optically pure.



(13)

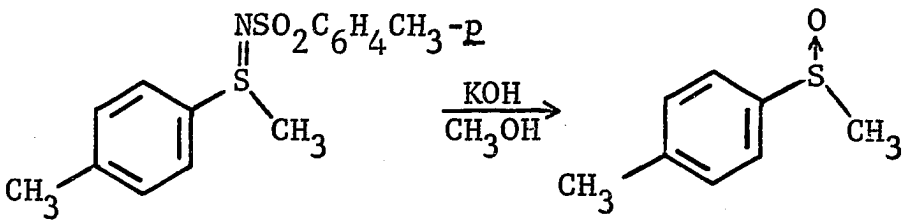
(+)-27 (-)-28



(14)

(-)-28 26

SCHEME III



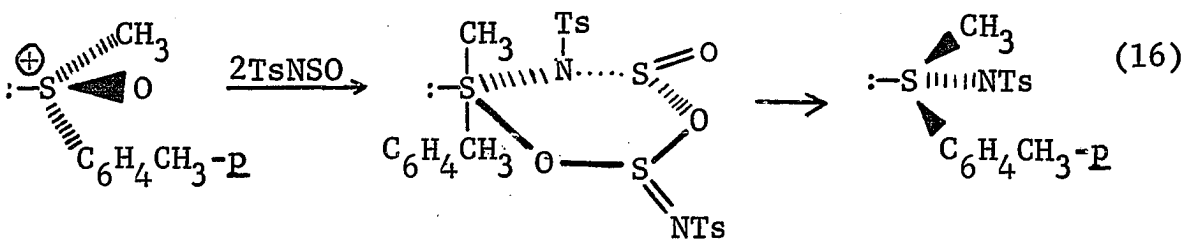
(15)

(-)-28 (+)-27

The relative configurations of (+)-27 and (-)-28 were established using optical rotatory dispersion (ORD) techniques. It was found that (+)-27 and (-)-28 gave curves with opposite signs of the Cotton effects. The similarity of the curves indicated that the same type of transition occurred in

both the sulfoxide (27) and the sulfilimine (28). Since the absolute configuration of (+)-27 had been previously determined as (R) (eq 8), the (S) configuration was assigned to (-)-28 on the basis of the ORD curves.

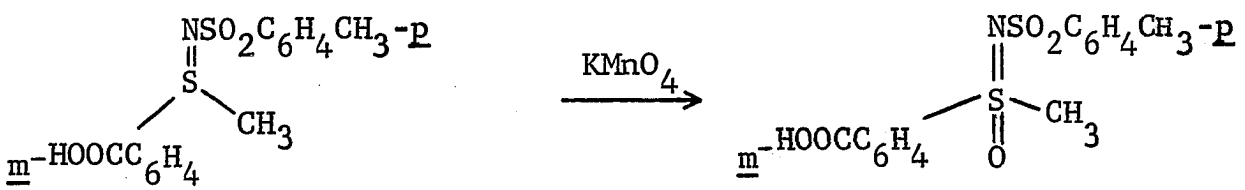
Having established the configuration of (-)-28 and (+)-27, reaction (13) can be said to proceed with inversion of configuration. Day and Cram[9] postulated the following reaction mechanism (eq 16).



(16)

(+)-(R)-27 (-)-(S)-28

Experimental evidence for the stereochemical course of the oxidation of sulfilimines to sulfoximines (eq 14) has been presented by Kresze and Wustrow.[10]



(17)

(+)-29 (+)-30

In an attempt to establish the stereochemical course of eq 17, Kresze and Wustrow[10] employed ORD techniques and

the Freudenberg Displacement Rule.[27] Under the conditions of the oxidation (eq 17), the sulfilimine 29, $[\alpha]_D$ +254°, yielded sulfoximine 30, $[\alpha]_D$ +143°. The ORD curves of both 29 and 30 are shown in Figure A.

It would appear from the ORD curves in Figure A that both 29 and 30 have the same configuration.

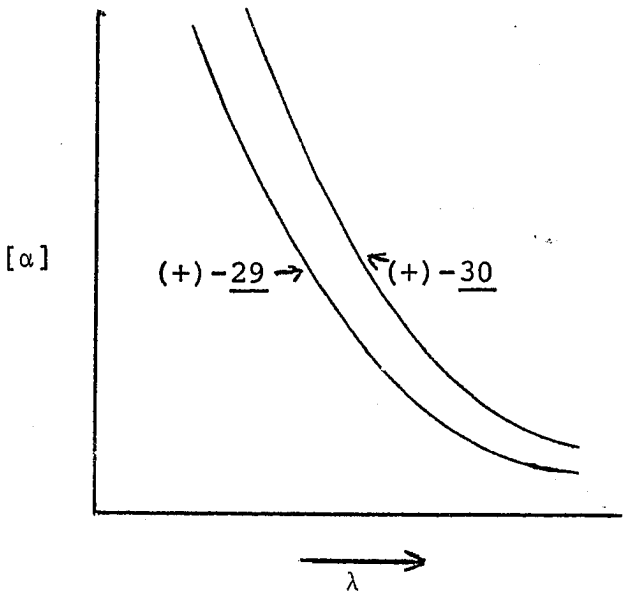


FIGURE A

Sulfilimine 29 and sulfoximine 30 were then converted to several derivatives. The derivatives and their D line rotations are shown in Table I.

	Sulfilimine $[\alpha]_D$, 29	Sulfoximine $[\alpha]_D$, 30
Acid	+254°	+143°
Na salt	+246°	+112°
Methyl ester	+243°	+133°
Amide	+259°	+149°

TABLE I

According to the Freudenberg Displacement Rule, "when similarly constituted dissymmetric compounds are chemically changed in the same way and the change produces a considerable shift in optical rotation in the same direction, then the two compounds probably have the same configuration."[28]

Since the D-line rotations of all the derivatives of 29 and 30 in Table I change considerably and in the same direction, sulfilimine 29 and sulfoximine 30 would appear to have the same configuration if the Freudenberg Displacement Rule can be applied to this system.

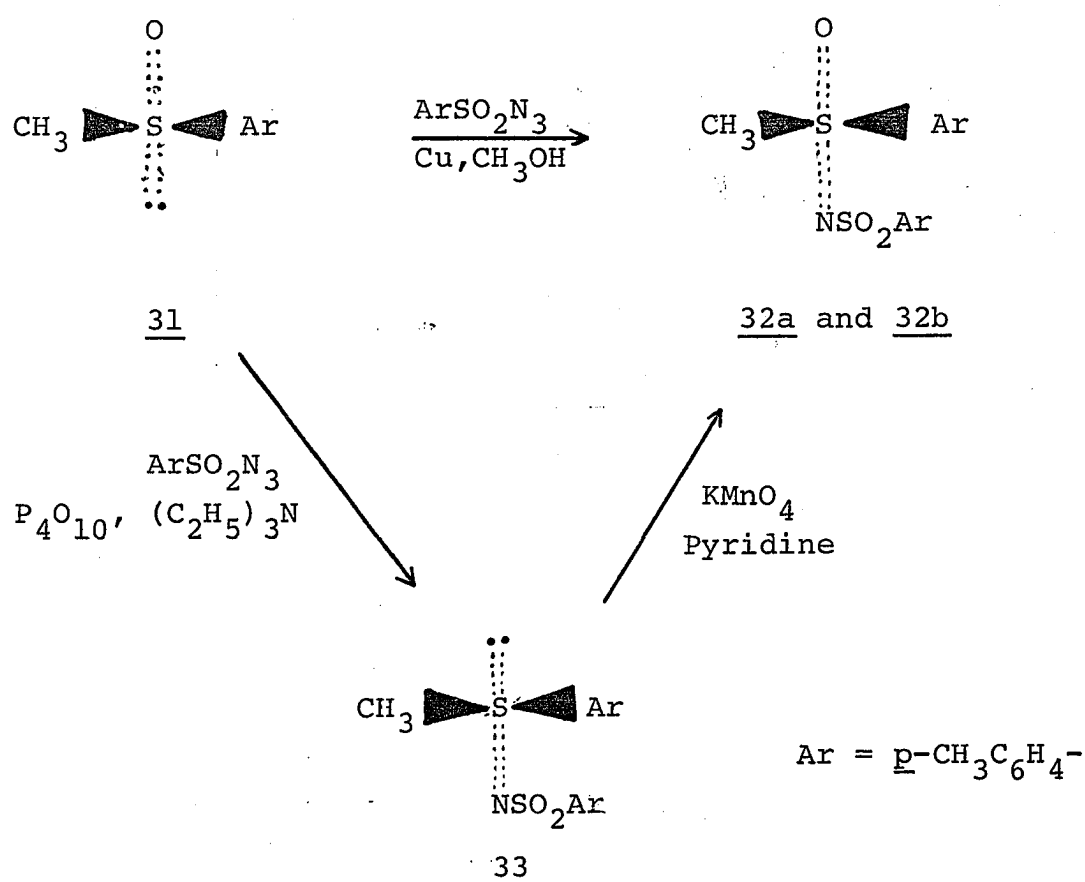
However, the above arguments in favor of similar configurations for 29 and 30 have a major weakness. Establishment of absolute configuration either by comparison of ORD curves or by the Freudenberg Displacement Rule requires that the two compounds being compared have similar structures at the asymmetric center. In the present case the structure of 29 involves asymmetry around a trigonal sulfur atom while 30 involves asymmetry around a tetragonal sulfur. The question is whether these structures can be considered similar enough to compare by these methods. To date this question has not been resolved.

However, the possibility remains that the relative configuration of 30 can be assigned validly from the configuration of 29 on the basis of a) the similarity of the ORD curves and b) the Freudenberg Displacement Principle. If the arguments presented by Kresze and Wustrow[10] are accepted, then 30 has the same configuration as 29 and it can

be said that the oxidation (eq 17) proceeds with retention.

It should be made clear that the above arguments should not be accepted as rigorous proof that the oxidation of sulfilimines to sulfoximines proceeds with retention; even Kresze and Wustrow[10] point out the shortcomings of these arguments. The arguments, however, do lend some support to the hypothesis that the oxidation occurs with retention.

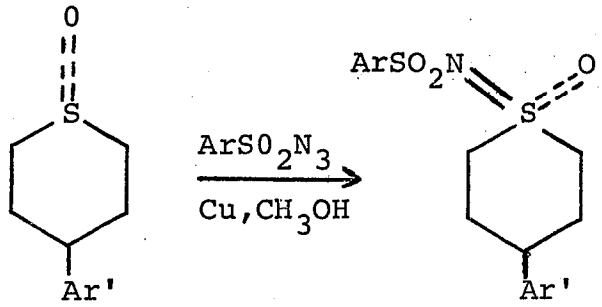
Now that the stereochemical course of reactions (13) and (14) have been discussed, the absolute configuration of the sulfoximine obtained from the Kwart-Kahn reaction can be assigned. The reaction sequence is represented in Scheme IV.



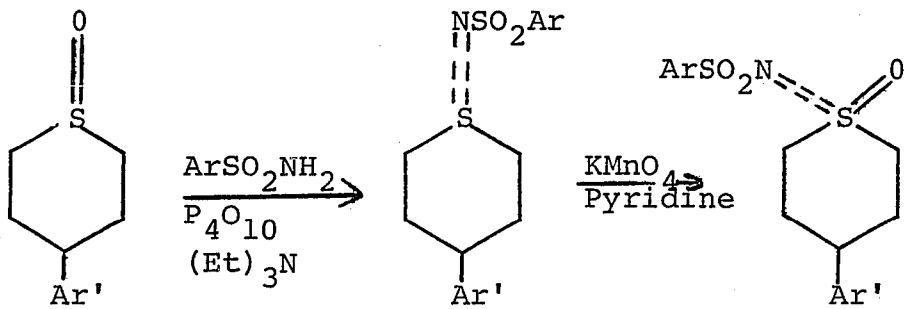
SCHEME IV

When (R)-methyl p-tolyl sulfoxide (31) (mp 74.5-75.5°, $[\alpha]_D$ +155° (c 1.6, acetone)) was treated[26] with p-toluenesulfonyl azide in the presence of copper, optically active S-methyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine (32a) (mp 158.5-159.5°, $[\alpha]_D$ -130° (c 1.6 acetone)) was obtained. The configuration of 32a was determined by conversion of (R)-methyl p-tolyl sulfoxide (31) to (S)-S-methyl-S-p-tolyl-N-p-toluenesulfonylsulfilimine (33) (mp 121-123°, $[\alpha]_{546}$ -84.1° (c 1.6, acetone)), a reaction shown[9] (p 23) to proceed with inversion of configuration. Sulfilimine 33 was then oxidized to the optically active sulfoximine 32b (mp 140-143°, $[\alpha]_D$ -28.8° (c 0.95, acetone)). If it is assumed (Arguments in favor of this assumption are presented on pp 23-26.) that conversion of 33 to 32b proceeded with retention of configuration, then conversion of 31 to 32a must also proceed with retention of configuration since the same isomer of 32 was obtained by both paths--as indicated by the signs of rotation at the D line (-130° and -28.8°). Sulfoximine 32 can be then assigned the (R) configuration. At the very least the conversions of 31 to 32a must follow the same stereochemical course.

In addition trans-4-(p-chlorophenyl)tetrahydrothiopyran-1-oxide (34) was treated[26] with p-toluenesulfonyl azide. The absolute configuration of the resulting sulfoximine (35) was established in a manner similar to the above. The reaction sequence is shown in Scheme V.



34 35



36 37 38

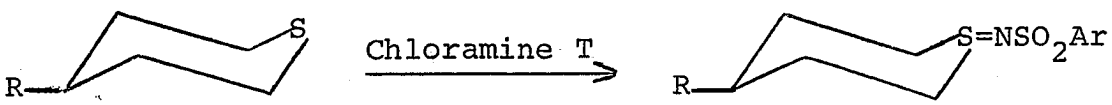
Ar=p-$CH_3C_6H_4$- , Ar'=p-ClC_6H_4-

SCHEME V

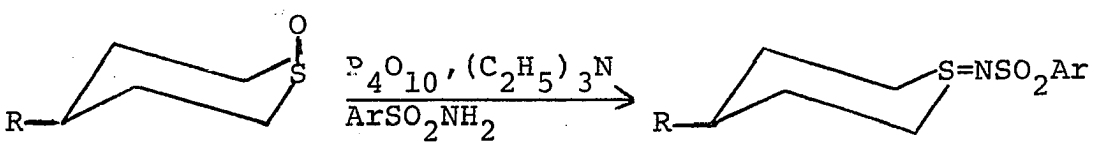
To establish the configuration of 35 (mp 226.5-227.5°) 4-p-chlorophenyltetrahydrothiopyran-1-oxide (36) was converted to the corresponding sulfilimine (37) by a reaction reported to proceed with inversion[9] (p 23). The sulfilimine (37) was then oxidized to the corresponding sulfoximine (38) (mp 188-188.5°). The difference in the melting points of sulfoximine 35 and sulfoximine 38 indicates that they are geometric isomers. If it is assumed

(Arguments in favor of this assumption are on pp 23-26.) that the oxidation proceeds with retention, then the conversion of 34 to 35 can be said to proceed with retention.

The stereochemical course of the conversion of S,S-4-(p-chlorophenyl)pentamethylene thiane (39) to S,S-4-p-(chlorophenyl)pentamethylene-N-p-toluenesulfonylsulfilimine (40) was also established[26] during the course of this work. This was accomplished by comparison of sulfilimine 40 (mp 214-215°) with sulfilimine 37 (mp 214-215°). Since the configuration of 37 has been shown[12] to be trans (p 28), the configuration of 40 can also be established as trans since the sulfilimines obtained from both reactions are identical in their physical properties.



39 40 (18)

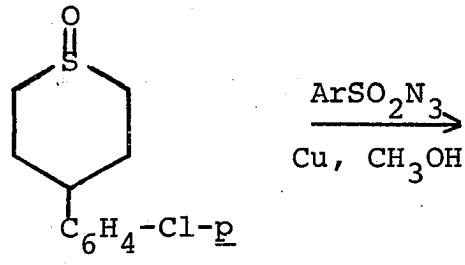


36 37 (19)

R = p-ClC_6H_4-

Ar = p-$CH_3C_6H_4$-

It should be noted that cis-4-(p-chlorophenyl)tetrahydrothiopyran-1-oxide (41) did not react when submitted to the conditions of the Kwart-Kahn reaction.

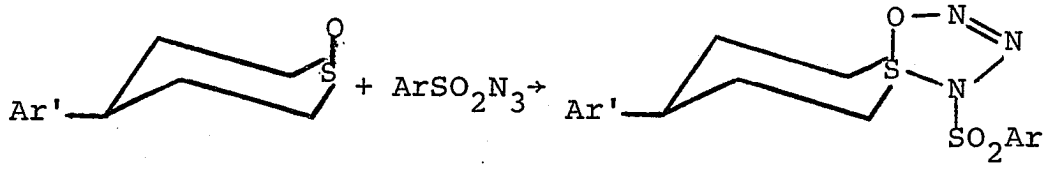


No Reaction (20)

Ar-p-$CH_3C_6H_4$-

41

It is not clear why this reaction did not take place. One possible reason might involve steric problems in the formation of the sulfoxide-azide complex (42) similar to 24 on page 21.



(21)

Ar=p-$CH_3C_6H_4$-; Ar'=p-ClC_6H_4-

42

However, it is not easy to see why there should be difficulty in forming complex 42.

Thus, from the reaction sequences illustrated in Scheme IV and Scheme V it can be concluded that the conversion of optically active sulfoxides to optically active sulfoximines by the Kwart-Kahn reaction results in stereochemical retention of configuration around the sulfur atom.

(+)-(R)-Ethyl p-tolyl sulfoximine ((+)-43) and (+)-(R)-isopropyl p-tolyl sulfoximine ((+)-44) were prepared from the corresponding (+)-(R) sulfoxides by the Kwart-Kahn reaction. Figures B-G contain the ORD, CD and uv spectra for the (R)-S-methyl-, (R)-S-ethyl-, and (R)-S-isopropyl-S-p-tolyl-N-p-toluenesulfonylsulfoximines (32, 43 and 44). The uv data for these sulfoximines and for the corresponding sulfoxides are listed in Table II.

The maximum at about 250 mμ (Table II) in the uv spectra of sulfoxides has been termed the "primary band".[19] The primary band was considered to arise from the interaction of the weak $\pi \rightarrow \pi^*$ transition and the sulfoxide $n \rightarrow \pi^*$ excitation. A (+) Cotton effect, which characterized sulfoxides of the (R) configuration, was associated with the primary band.

The primary band in the uv for sulfoximines occured in the vicinity of 228 mμ (Table III, Figures B-D). In all three alkyl p-tolylsulfoximines this band was associated with an optically active absorption (Figures E-G). The minus sign of the Cotton effect characterized the (R) configuration of the sulfoximine.

Figure B. Uv Spectrum of (R)-S-Methyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine

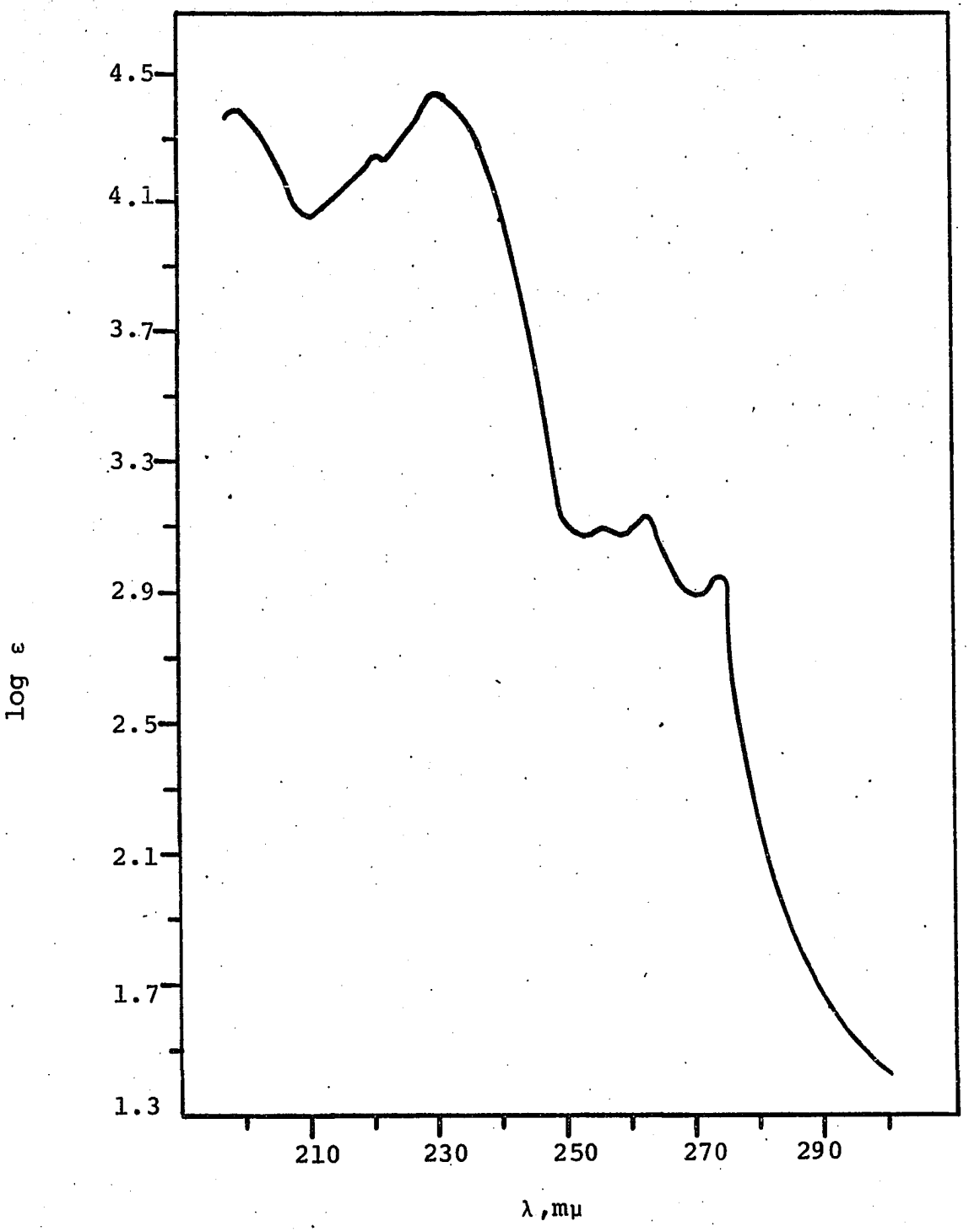


Figure C. Uv Spectrum of (R)-S-Ethyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine

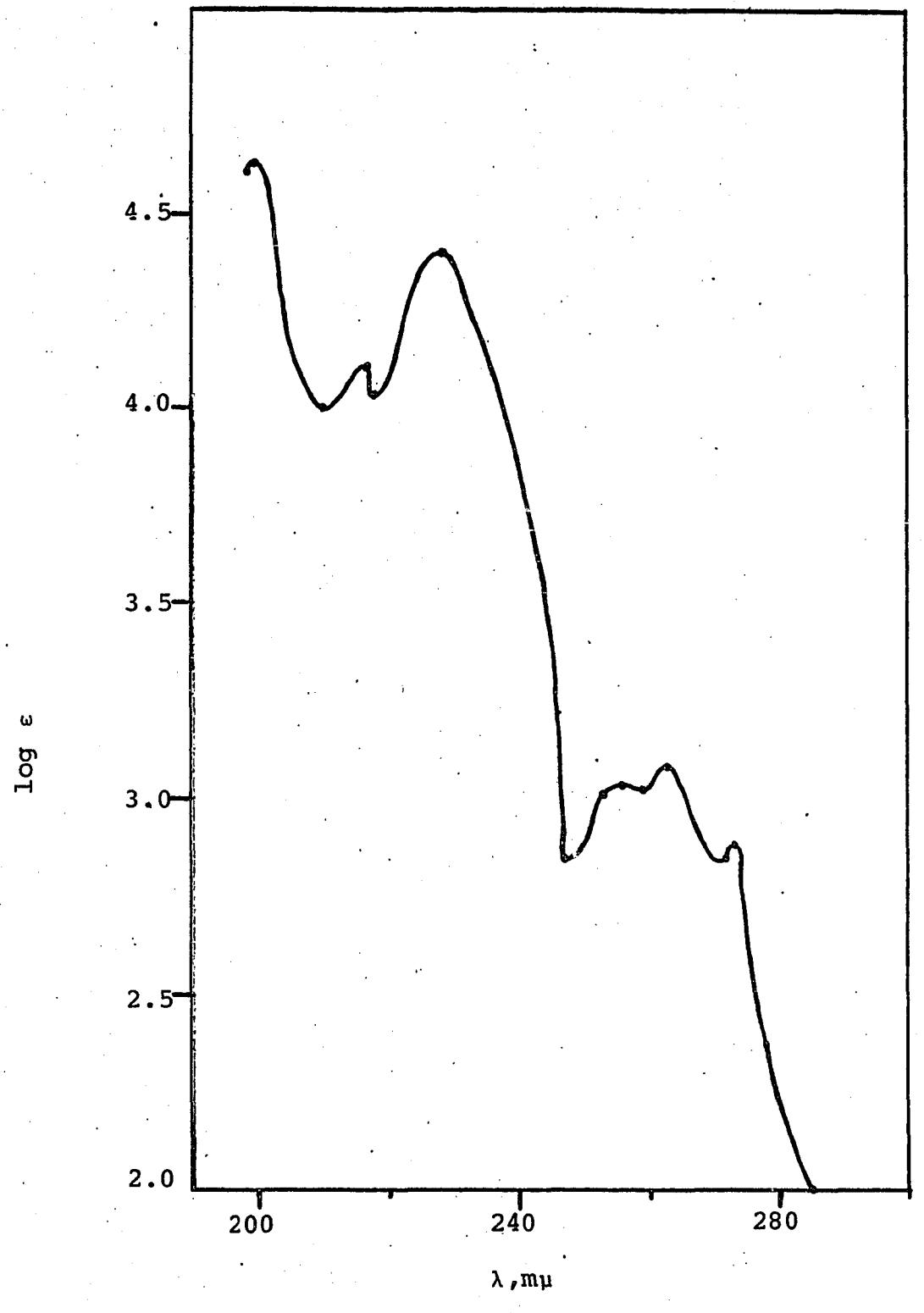


Figure D. (R)-S-Isopropyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine

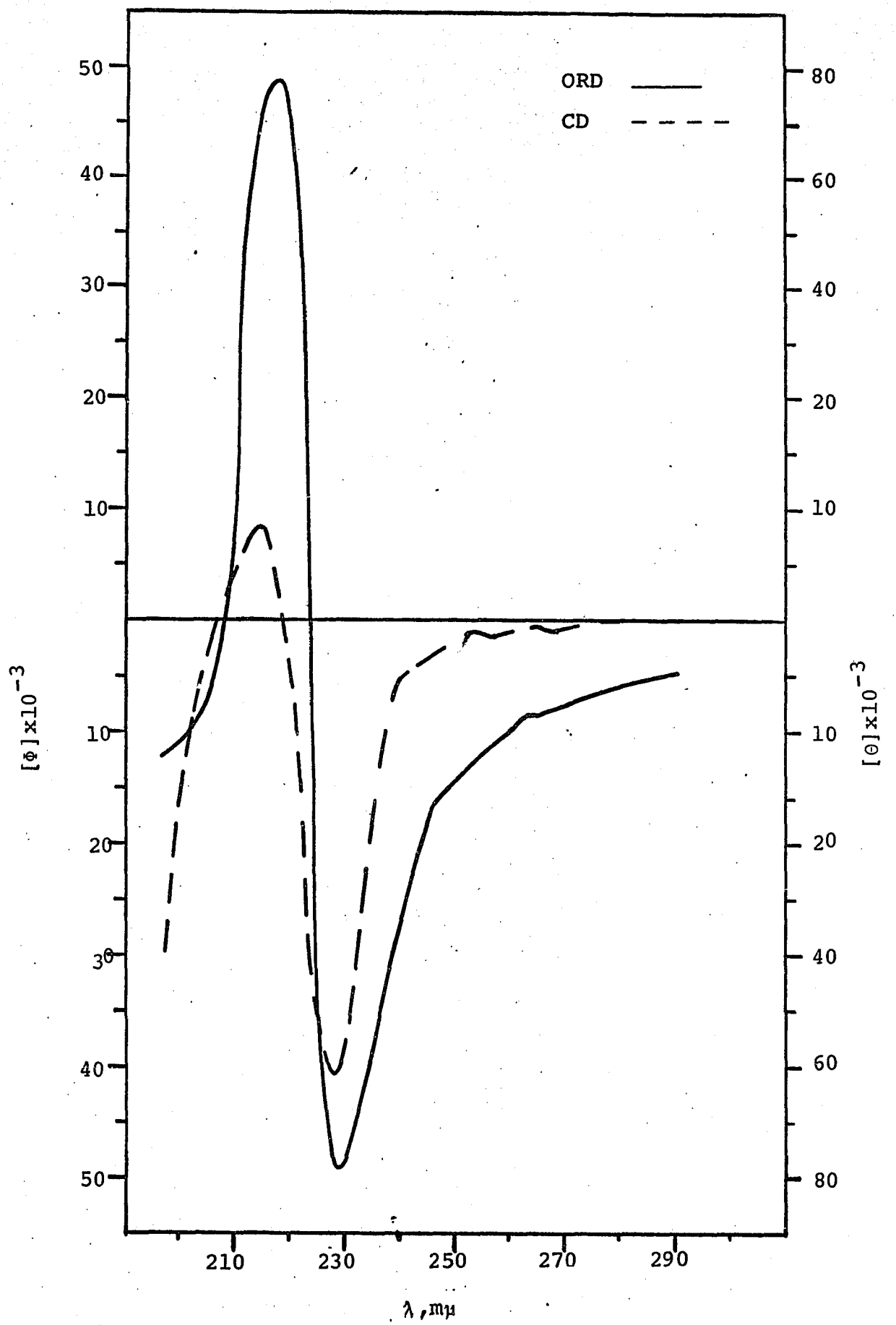


Figure E. ORD and CD Curves of (R)-S-Methyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine

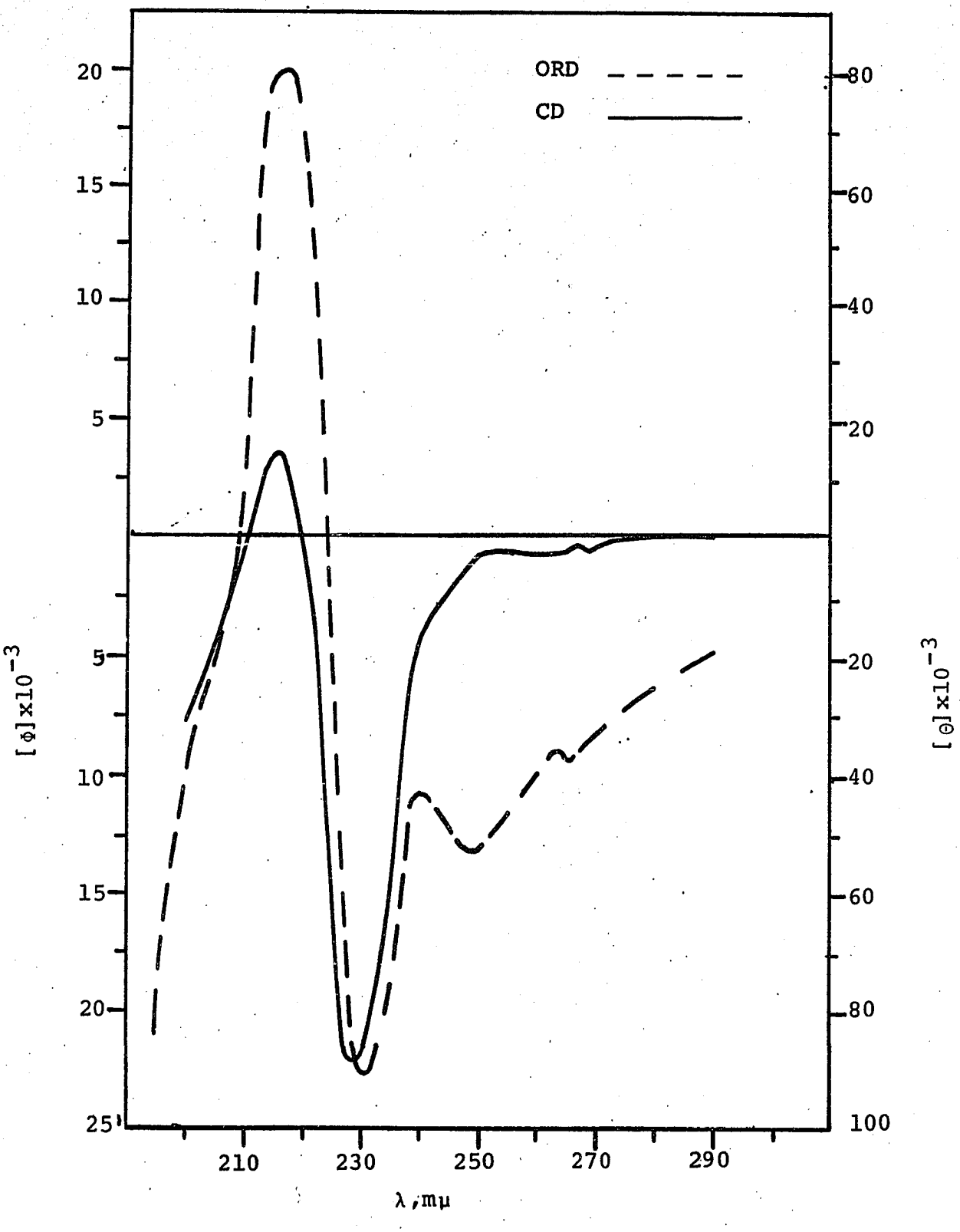


Figure F. ORD and CD Curves of (R)-S-Ethyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine

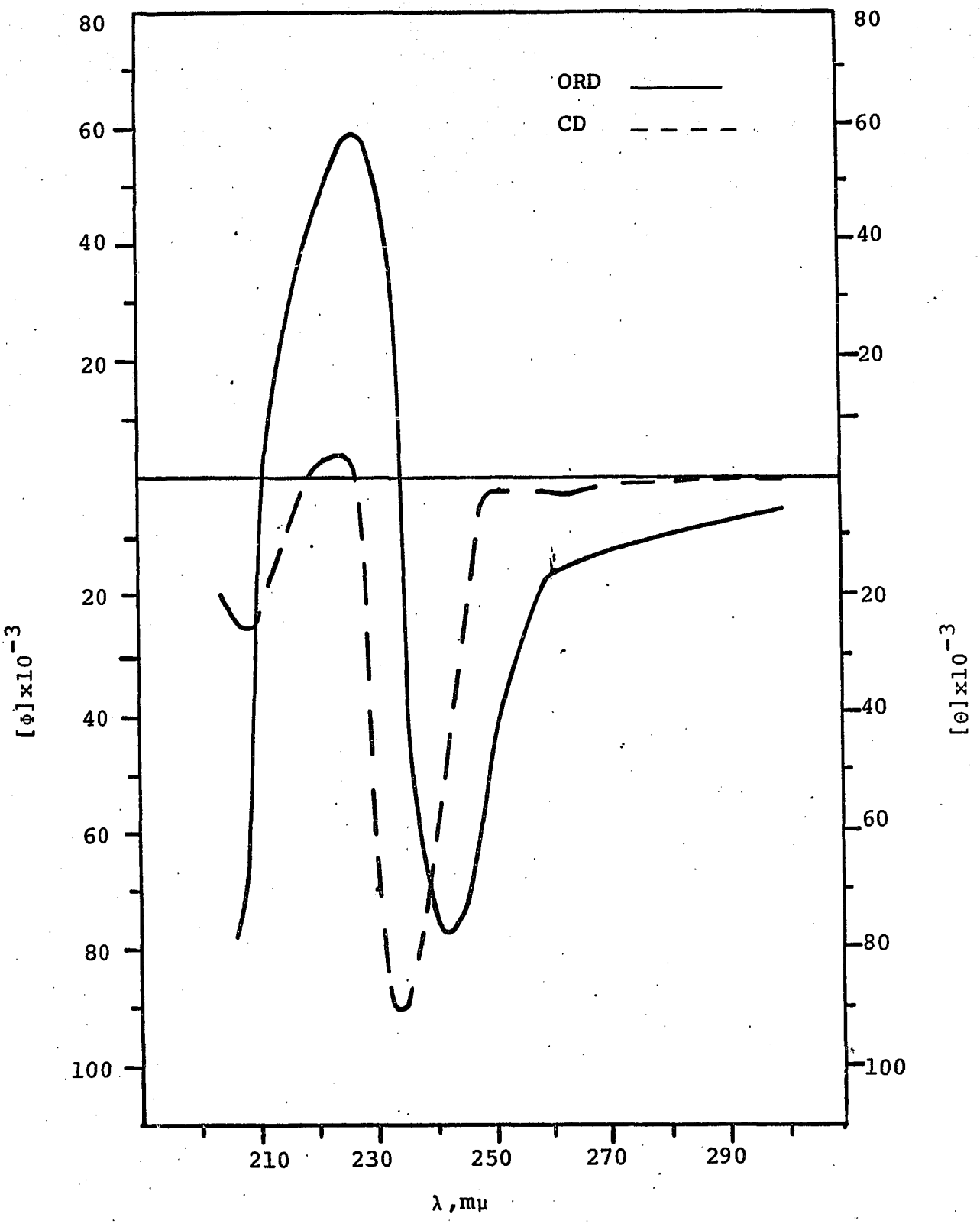


Figure G. ORD and CD Curves of (R)-S-isopropyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine

Table II

Ultraviolet Absorption of Alkyl Aryl Sulfoxides and Sulfoximines

No.	R, in p-CH_3-C_6H_4SOR	Solvent[a]	Absorption Characteristics[b]					
	Methyl[c]	I	278 (650)	268.5 (1670)	249 (4830)	217 (9330)	210 (10400)	
	Ethyl[c]	I	279 (750)	270 (1840)	251 (4980)	218 (9390)	210 (10200)	
	Isopropyl[c]	I	270 (2620)	265 (3500)	254.6 (4800)	217.6 (9300)	210.7 (9740)	
	R, in p-CH_3-$C_6H_4S(O)(NTs)R$							
32	Methyl	E	275.0 (800)	262.9 (1245)	256.2 (1112)	228.3 (25600)	220.3 (18000)	199.7 (46400)
43	Ethyl	E	273.2 (944)	262.5 (1404)	255.8 (1269)	228.5 (28220)	219.2 (18000)	199.6 (24500)
44	Isopropyl	E	273.9 (780)	263 (1220)	256.2 (1097)	228.7 (24950)	217.0 (12900)	203.1 (43500)

[a]I, isooctane; E, absolute ethanol. [b]Wavelengths in mμ, molecular extinction coefficients (ε) in parentheses; maxima are underlined; all other values refer to shoulders or inflections. [c]Reference 19.

Table III

Optical Rotatory Dispersion and Circular Dichroism of Alkyl Aryl Sulfoximines

R, in p-CH_3-$C_6H_4S(O)(NTs)R$	Solvent[a]	ORD Characteristics[b]					
		tr	pk	tr	z[c]	pk	z
Methyl	E	274 (-8725)	273 (-8726)	245 (-38100)	234	228 (+48200)	217
Ethyl	E	276 (-9393)	274 (-9169)	241 (-22600)	229	227 (+20200)	219
Isopropyl	E	___	___	242.5 (-77200)	235	227.6 (+59700)	210

R, in p-CH_3-$C_6H_4S(O)(NTs)R$	Solvent[a]	CD Characteristics[d]					
Methyl	E	275 (-1100)	267 (-2040)	237 (-81800)	228.5	225 (+17900)	217
Ethyl	E	279 (-2000)	270 (-2900)	239 (-88000)	229	226 (+15000)	220.5
Isopropyl	E	___	264 (-2000)	235 (-90000)	228	225 (+6000)	219

[a]E, absolute ethanol. [b]Wavelengths in mμ; molecular rotation in parentheses; maxima are underlined; tr, trough; pk, peak. [c]Points at which the zero rotation axis is crossed. [d]Wavelengths in mμ; molecular ellipticities in parentheses; maxima are underlined.

Since the publication[26] of the above work, two other works dealt with the correlation of configurations of sulfoxides, sulfilimines, and sulfoximines.

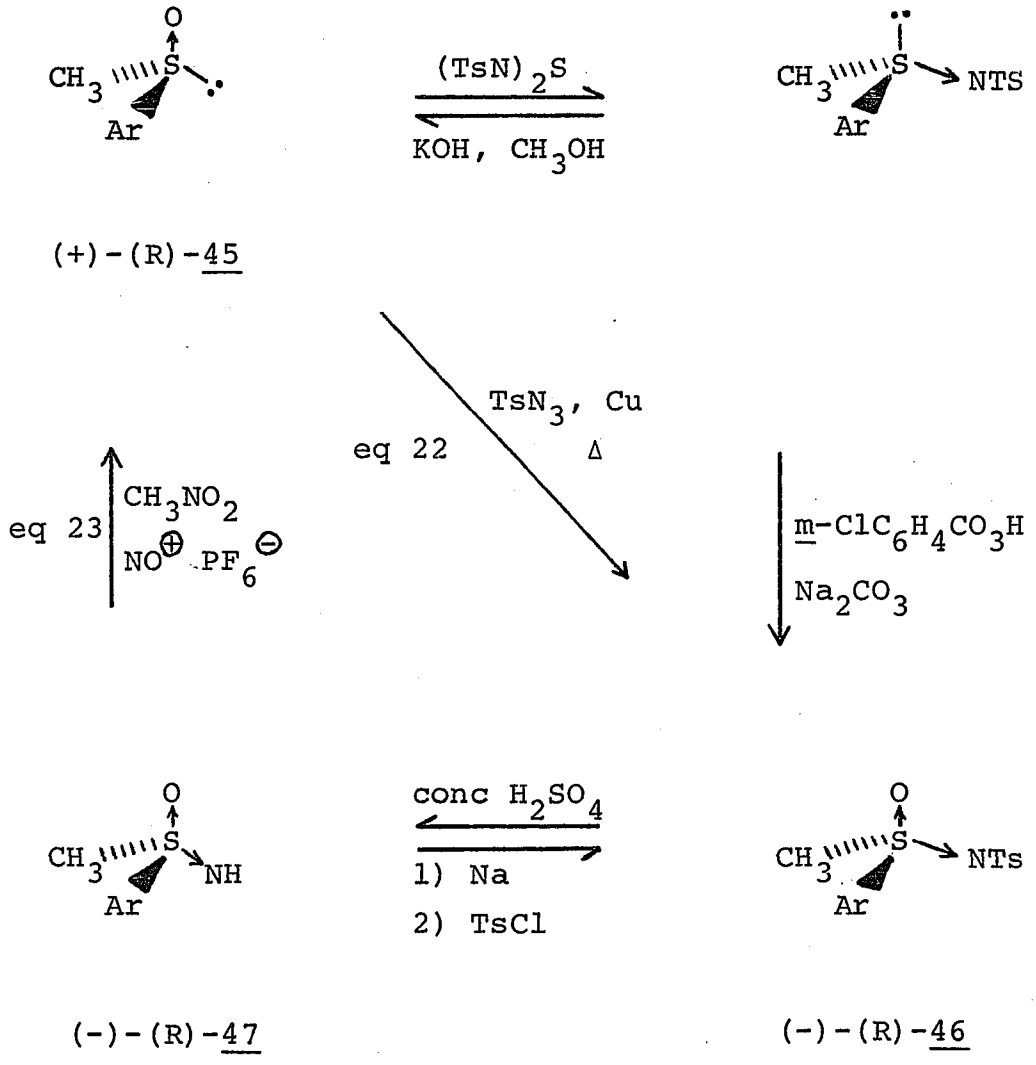
In the first paper,[29] (+)-(R)-methyl p-tolyl sulfoxide (45) was converted to (-)-(R)-S-methyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine (46) by means of the Kwart-Kahn reaction (eq 22 in Scheme VI). This report of the conversion of an (R)-sulfoxide to an (R)-sulfoximine with retention of configuration substantiated the results which have been illustrated in Scheme IV and Scheme V of this Thesis.

In addition, the same paper[29] reports other reactions which are useful in establishing configurations at the sulfur atom. These reactions are shown in Scheme VI.

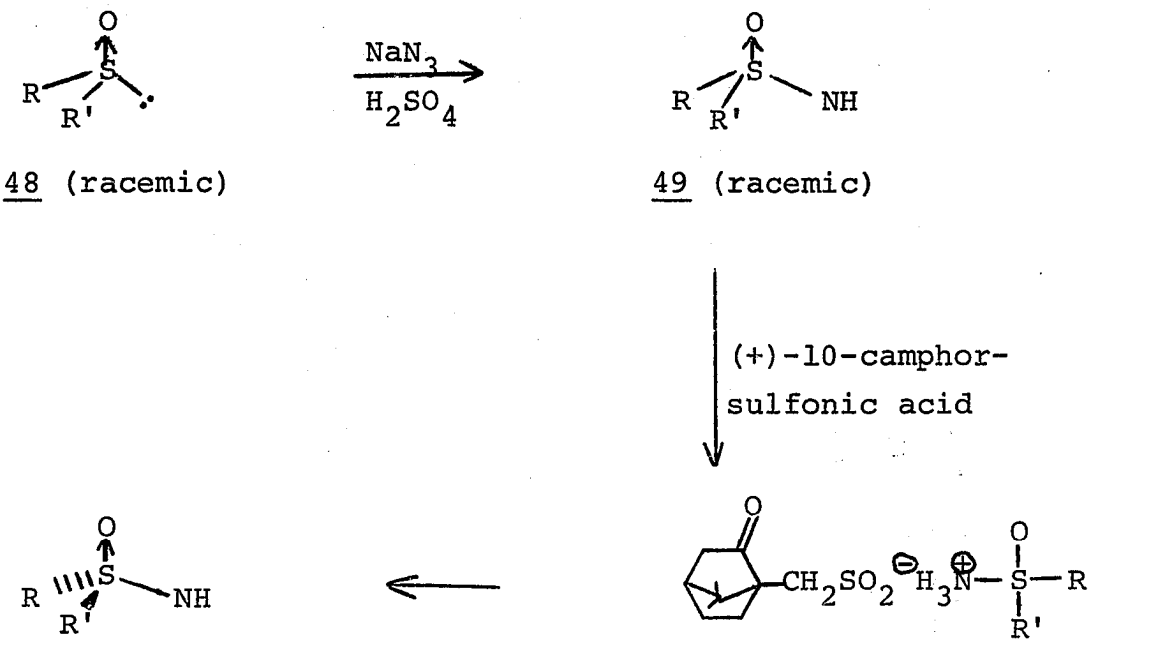
The conversion of (-)-(R)-47 to (+)-(R)-45 in Scheme VI (eq 23) is the first report of the conversion of an optically active sulfoximine (47) to an optically active sulfoxide (45). The reaction is reported to occur with at least 98% stereospecificity. Since the sulfoxide group is presumably displaced from the nitrogen atom by the nitrosyl hexafluorophosphate, the reaction probably proceeds with retention of configuration at sulfur.

The discovery of the conversion of 47 to 45 provides a good route for the preparation of optically active sulfoxides which are not available by other routes. Racemic sulfoxides (48) can be converted to racemic sulfoximines (49)

by reaction with hydrazoic acid.[12] The sulfoximines can then be resolved by salt formation (50) with optically active sulfonic acids. After decomposition of the salts, the optically active sulfoximines (51) can be converted to optically active sulfoxides (52) with nitrosyl hexafluorophosphate. The sequence of reactions is shown in Scheme VII.



Scheme VI



48 (racemic)

49 (racemic)

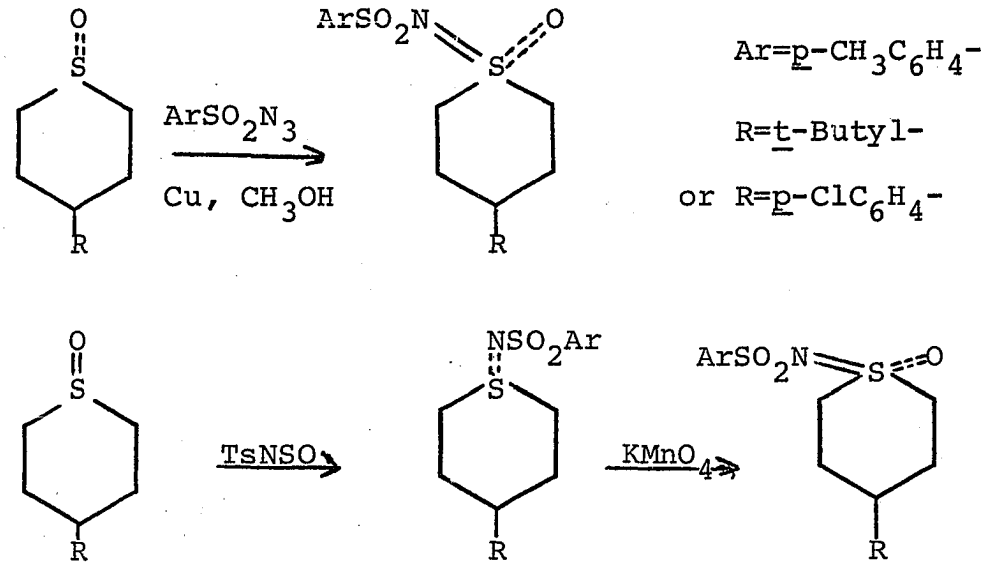
50 (separate diastereomers)

51 (either of two diastereomers)

52

Scheme VII

The second work[30] that dealt with stereochemical relationships among sulfoxides, sulfilimines, and sulfoximines is shown in the following sequence of reactions (Scheme VIII, R = t-butyl).



SCHEME VIII

The conclusions of Johnson,[30] shown in Scheme VIII (R = t-butyl), support the conclusions presented in this Thesis (Scheme VIII, R = p-chlorophenyl) excellently. It can be seen from Scheme VIII that the conversion of sulfoxides to sulfoximines by the Kwart-Kahn reaction was reported to proceed with retention of configuration at sulfur.

EXPERIMENTAL

The infrared absorption spectra were determined using a Perkin-Elmer Model 337 grating infrared spectrophotometer.

The ultraviolet absorption spectra were measured with a Cary 14 recording spectrophotometer.

Mass spectra were recorded by Miss Ta-Yuen Li on a Hitachi-Perkin Elmer RMU-6E mass spectrometer.

Optical rotations were measured on a Carl Zeiss photoelectric polarimeter.

Optical rotatory dispersion curves and circular dichroism curves were determined on a Cary Model 60 recording spectrophotometer.

Microanalyses were performed by Mr. Ingo Hartmann using the F & M Corp. Model 185 Carbon, Hydrogen, Nitrogen Analyzer.

Sodium p-Toluenesulfinate Dihydrate.[31] p-Toluenesulfonyl chloride (572 g, 3.00 mole) was ground in a mortar. Water (3 l.) was placed in a 4 l. beaker provided with a mechanical stirrer and rubber tubing for passing steam directly into the water. Steam was passed into the water until the temperature reached 70°. The steam was shut off and zinc dust (390 g, 6.00 g-atoms) was added. The sulfonyl chloride was then added in small portions over a ten-minute period. Stirring was continued for ten minutes after the last of the sulfonyl chloride had been added. Steam was passed into the mixture until the temperature reached 90°. The steam was shut off, and sodium carbonate (318 g, 3.00 mole) was added in small portions to avoid frothing. Aqueous 10 N sodium hydroxide was added until the solution was strongly alkaline. The mixture was separated by filtration and the cake of excess zinc dust and zinc compounds was transferred to a beaker and mixed with water (1 l.). Steam was passed into the stirred mixture until frothing started. The steam was shut off but the stirring was continued for ten minutes. The mixture was filtered and the filtrate was added to the mother liquid in a large evaporating dish. The solution was concentrated until crystallization occurred around the edges. The solution was cooled and the white crystals were collected by filtration. The crystals (558 g, 86.9%) were air-dried and stored.

p-Toluenesulfinyl Chloride.[32] Powdered sodium p-

toluenesulfinate dihydrate (214 g, 1.00 mole) was added in portions to a round-bottomed flask containing thionyl chloride (812 g, 7.00 mole) at room temperature over a period of one hour. The temperature rose at first but soon dropped to 0° as the addition proceeded. The reaction mixture, a yellow liquid containing a white solid, was protected from moisture by means of a calcium chloride drying tube, and was set aside at room temperature for five hours. The excess thionyl chloride was removed under reduced pressure at 50°. The last traces of thionyl chloride were removed by addition of 50-ml portions of anhydrous ether, followed by distillation at aspirator pressure. The crude p-toluenesulfinyl chloride was dissolved in anhydrous ether and filtered by suction under a nitrogen atmosphere. The inorganic solid was washed with several portions of anhydrous ether and the ether solution was concentrated until a heavy oil (155 g, 88.9% (crude)) was obtained.

(-)-Menthyl (-)-p-Toluenesulfinate.[16] p-Toluenesulfinyl chloride (155 g, 0.889 mole) was diluted with anhydrous ether (200 ml) and added to a 1000-ml three-necked flask provided with a mechanical stirrer, an addition funnel, and a reflux condenser with a calcium chloride drying tube. A solution of (-)-menthol (139 g, 0.891 mole) and anhydrous pyridine (75 g, 50 ml, 0.95 mole) in anhydrous ether (100 ml) was added dropwise at -5° to 0° over a two-hour period. The reaction mixture was warmed to room temperature and 5% aqueous

hydrochloric acid (100 ml) was added dropwise over a one-hour period. After separation of the layers, the organic layer was washed twice with 5% hydrochloric acid (100 ml), once with aqueous sodium carbonate (100 ml), twice with distilled water (100 ml), and finally dried over anhydrous magnesium sulfate. After filtering, the ether solution was concentrated. Tetraethylammonium chloride (0.1 g) was added and hydrogen chloride gas was bubbled in slowly for about five minutes. The solution was cooled with a Dry Ice-acetone bath. Crystals were obtained. After filtration, the filtrate was concentrated to a smaller volume and treated as above with tetraethylammonium chloride and hydrogen chloride gas. This process was repeated until crystallization ceased. The crude ester was recrystallized three times from acetone-water (4:1) and stored in a desiccator. The pure ester (161 g, 63.5%) was obtained as white crystals (mp 104-105.5°, lit.[33] mp 106-107°, and $[\alpha]_D^{24}$ -199.0° (c 0.200, acetone), lit.[33] $[\alpha]_D^{25}$ -199.2° (c 2.0, acetone)).

(+)-(R)-Methyl p-Tolyl Sulfoxide.[19] The Grignard reagent, prepared from methyl iodide (14.2 g, 0.100 mole) and oven-dried magnesium turnings (2.43 g, 0.100 g-atom) in anhydrous ether (75 ml), was added dropwise with mechanical stirring and cooling (ice-salt bath) to a solution of (-)-menthyl (-)-p-toluenesulfinate (21.3 g, 0.0725 mole) in anhydrous ether (200 ml). The addition was carried out under a slow stream of sulfuric acid-dried nitrogen. After stirring

for one hour at ice-bath temperature, the reaction mixture was hydrolyzed with saturated aqueous ammonium chloride (200 ml). The layers were separated and the ether layer was washed once with 10% hydrochloric acid solution, twice with 10% sodium carbonate solution and twice with water. The organic layer was concentrated and the remaining orange oil was steam-distilled from a 20% potassium hydroxide solution. The distillate was extracted with ether and the ether layers were dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure, and the solid residue was dissolved in anhydrous ether. After concentrating the ether solution, it was cooled in a Dry Ice-acetone bath and the crystals were collected by filtration. The crystals were dissolved in a small volume of ether. The solution was clarified with Norit A, and, upon cooling, white crystals formed which were collected. The desired sulfoxide (4.1 g, 27%) was dried in a vacuum desiccator, mp 75.0-75.5°; $[\alpha]_D^{25}$ +155° (c 1.60, acetone), lit.[19] mp 73-74.5°; lit.[34] $[\alpha]_D^{24}$ +156° (acetone).

(R)-S-Methyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine (32a) from (+)-(R)-Methyl p-Tolyl Sulfoxide. (+)-(R)-Methyl p-tolyl sulfoxide (1.15 g, 0.00746 mole, $[\alpha]_D^{25}$ +155° (c 1.6, acetone)), p-toluenesulfonyl azide (3.0 g, 0.015 mole), freshly reduced copper (0.10 g, 0.0016 g-atom), and anhydrous methanol (75 ml) were heated under reflux for 48 hours. After the solution was cooled to room temperature, a slightly basic

solution of ethylenediaminetetraacetic acid (0.47 g, 0.0016 mole) was added dropwise. Chloroform was added, followed by the addition of water until two layers, chloroform and aqueous methanol, formed. The methanol layer was extracted with chloroform and the chloroform extracts were dried over anhydrous magnesium sulfate. After filtration and removal of solvent, a yellow oil was obtained which crystallized on standing. After crystallization from methanol, white crystals were obtained (mp 158.5-159.5°; $[\alpha]_D^{23}$ -130° (c 2.00, acetone), $[\alpha]_{578}^{23}$ -136° (c 2.00, acetone), $[\alpha]_{546}^{23}$ -156° (c 2.00, acetone)).

Uv Data: see Figure B (p32) and Table II (p38).

ORD Data: see Figure E (p 35) and Table III (p 39).

CD Data: see Figure E (p 35) and Table III (p 39).

Mass Spectral Data: see Figure H in Appendix (p 63).

Anal. Calcd for $C_{15}H_{17}NO_3S_2$: C, 55.70; H, 5.29; N, 4.33. Found: C, 55.96; H, 5.42; N, 4.43.

Purification of (+)-(R)-Ethyl p-Tolyl Sulfoxide. Crude (+)-(R)-ethyl p-tolyl sulfoxide (1.5 g, 0.0088 mole), $[\alpha]_D^{25}$ +174.8° (c 2.6, acetone)) was distilled (bp 96-98° (0.3-0.35 mm)) to give (+)-(R)-ethyl p-tolyl sulfoxide (0.7 g, $[\alpha]_D^{28.8}$ +186.5° (c 1.15, acetone)) (lit.[19] bp 94° (0.4 mm); $[\alpha]_D$ +187.5° (acetone)).

(R)-S-Ethyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine (43). (+)-(R)-Ethyl p-tolyl sulfoxide (0.60 g, 0.0036 mole), p-toluenesulfonyl azide (1.0 g, 0.0051 mile), freshly reduced copper

(0.10 g, 0.0016 g-atom), and anhydrous methanol were heated under reflux overnight. After the solution was cooled to room temperature, a slightly basic solution of ethylenediaminetetraacetic acid (0.47 g, 0.0016 mole) was added dropwise. Chloroform was added, followed by addition of water until two layers (chloroform and methanol) formed. The methanol layer was extracted with chloroform and the extracts were dried over anhydrous magnesium sulfate. After filtration and removal of solvent, an oil was obtained which was chromatographed on a column (32 cm long, 3 cm diameter) of alumina (Fisher, Neutral, Brockman Activity I, 80-200 mesh) using acetonitrile as eluent. The oil that was obtained crystallized after it was seeded with a crystal of S-methyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine and refrigerated. The product (0.11 g, 9.2%) was obtained as white powder (mp 50.5-51.5°; $[\alpha]_D^{29.3}$ -162° (c 0.99, chloroform), $[\alpha]_{578}^{29.3}$ -170° (c 0.99, chloroform), $[\alpha]_{546}^{29.3}$ -195° (c 0.99, chloroform)).

Uv Data: see Figure C (p 33) and Table II (p 38).

ORD Data: see Figure F (p 36) and Table III (p 39).

CD Data: see Figure F (p 36) and Table III (p 39).

Mass Spectral Data: see Figure I in Appendix (p 64).

(+)-(R)-Isopropyl p-Tolyl Sulfoxide.[19] The Grignard reagent prepared from 2-bromopropane (12.3 g, 0.100 mole) and oven-dried magnesium turnings (2.43 g, 0.100 mole) in anhydrous

ether (125 ml) was titrated with 1.00 N sec-butanol in xylene using 1,10 phenanthroline as an indicator. The solution was found to contain 0.032 mole of Grignard. This was added dropwise with mechanical stirring to a solution of (-)-menthyl (-)-p-toluenesulfinate (9.0 g, 0.031 mole) which had been heated to reflux. The addition was carried out under a slow stream of sulfuric acid-dried nitrogen. After stirring for 2.5 hours at reflux temperature, the reaction mixture was hydrolyzed with 10% hydrochloric acid solution. The mixture was then washed once with 10% hydrochloric acid solution, twice with 10% sodium carbonate and twice with water. The organic layer was steam-distilled from a 20% potassium hydroxide solution. The distillate was extracted with ether and the ether layers were dried over anhydrous magnesium sulfate. After filtration and concentration of the ethereal solution, the remaining oil was vacuum distilled. The sulfoxide (0.90 g, 15%) boiled at 120° (1.5 mm), $[\alpha]_D^{30.5}$ +177°, (c 2.81, acetone) (lit.[19] bp 100° (0.07 mm); $[\alpha]_D$ +176.5° (acetone)).

(R)-S-Isopropyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine (44). (R)-Isopropyl p-tolyl sulfoxide (0.9 g, 0.005 mole), p-toluenesulfonyl azide (1.2 g, 0.0061 mole), freshly reduced copper (0.10 g, 0.0016 g-atom), and anhydrous methanol were heated under reflux overnight. After the solution was cooled to room temperature, a slightly basic solution of ethylenediaminetetraacetic acid (0.47 g, 0.0016 mole) was added dropwise. Chloroform was added, followed by addition of water

until two layers (chloroform and aqueous methanol) formed. The methanol layer was extracted with chloroform and the extracts were dried over anhydrous magnesium sulfate. After filtration and removal of solvent, an oil was obtained which was chromatographed on a column (32 cm long, 3 cm diameter) of alumina (Fisher, Neutral, Brockman Activity I, 80-200 mesh) using acetonitrile as eluent. The oil obtained was seeded with a crystal of S-methyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine and refrigerated. The product (300 mg, 18.6%) was obtained as a white powder (mp 110.5-112.5); $[\alpha]_D^{28.3}$ -214° (c 0.89, chloroform), $[\alpha]_{578}^{28.3}$ -226° (c 0.89, chloroform), $[\alpha]_{546}^{28.3}$ -260° (c 0.89, chloroform)).

Uv Data: see Figure D (p 34) and Table II (p 38).

ORD Data: see Figure G (p 37) and Table III (p 39).

CD Data: see Figure G (p 37) and Table III (p 39).

Mass Spectral Data: see Figure J in Appendix (p 65).

Anal. Calcd for $C_{17}H_{21}NO_3S_2$: C, 58.09; H, 6.02; N, 3.98. Found: C, 57.94; H, 6.04, N, 3.99.

(S)-S-Methyl-S-p-tolyl-N-p-toluenesulfonylsulfilimine (33). p-Toluenesulfonamide (1.2 g, 0.0070 mole), triethylamine (2.1 g, 0.021 mole), and phosphorous pentoxide (1.3 g, 0.0090 mole), were dissolved in anhydrous methylene chloride (40 ml) and the solution was cooled to 0°. (R)-methyl p-tolyl sulfoxide (1.0 g, 0.0065 mole, $[\alpha]_D$ +155° (c 1.6, acetone)), dissolved in a minimum amount of anhydrous methylene chloride, was added dropwise. The reaction mixture

was stirred for 11 hours at 0° and for three hours at room temperature. The methylene chloride was decanted, the solvent was removed and the residue was chromatographed on a column (32.5 cm long, 3 cm in diameter) of alumina (Fisher, Neutral, Brockman Activity I, 80-200 mesh). Acetonitrile was used as eluent. The product (0.46 g, 17%) was obtained as white crystals (mp 121-123°, $[\alpha]_D^{24.5}$ -84.1° (c 1.6, acetone)).

Anal. Calcd for $C_{15}H_{17}NO_2S_2$: C, 58.60; H, 5.57; N, 4.71. Found: C, 58.90; H, 5.74; N, 4.71.

(R)-S-Methyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine (32b) from (S)-S-Methyl-S-p-tolyl-N-p-toluenesulfonylsulfilimine (33). (S)-S-Methyl-S-p-tolyl-N-p-toluenesulfonylsulfilimine (0.43 g, 0.0014 mole), potassium permanganate (4.4 g, 0.0028 mole), and anhydrous pyridine (30 ml) were stirred at room temperature for six days. The reaction mixture was decolorized with sodium bisulfite and extracted with chloroform. The extracts were washed with dilute hydrochloric acid (5%) and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was removed under reduced pressure. A white oil was obtained which was diluted with a small amount of chloroform and chromatographed on a column (32 cm long, 3.0 cm diameter) of silica gel (Fisher, Powder), using spectral chloroform as eluent. The product (0.21 g, 46%) was obtained as white crystals (mp 140-142°, $[\alpha]_D^{23.5}$ -28.8°). The infrared spectrum was identical with that

of 32a.

S,S-4-(p-Chlorophenyl)pentamethylene-N-p-toluenesulfonylsulfoximine (35) from trans-4-p-Chlorophenyltetrahydrothiopyran-1-oxide (34). trans-4-p-Chlorophenyltetrahydrothiopyran-1-oxide (0.5 g, 0.002 mole), freshly reduced copper (0.1 g, 0.002 mole) and p-toluenesulfonyl azide (1.5 g, 0.0076 mole) were added to 60 ml of anhydrous methanol in a 250-ml three-necked flask fitted with a dropping funnel, condenser, and mechanical stirrer. The solution was heated under reflux overnight. After the dark green solution had cooled to room temperature, a slightly basic solution of ethylenediaminetetraacetic acid (0.71 g, 0.0024 mole) was added dropwise. Chloroform was added, followed by the addition of water until two layers (chloroform and aqueous methanol) formed. The methanol layer was extracted with chloroform and the chloroform extracts were dried over anhydrous magnesium sulfate. After filtration and removal of solvent, an oil remained which was seeded with a crystal of authentic S,S-4-(p-chlorophenyl)-pentamethylene-N-p-toluenesulfonylsulfoximine (mp 226.5-227.5°; 0.071 g, 9.0%).

Anal. Calcd for $C_{18}H_{20}ClNO_3S_2$: C, 54.33; H, 5.06, N, 3.52. Found: C, 54.22; H, 5.09; N, 3.60.

Attempted Preparation of S,S-4-(p-Chlorophenyl)pentamethylene-N-p-toluenesulfonylsulfoximine from cis-4-p-Chlorophenyltetrahydrothiopyran-1-oxide (41). cis-4-p-Chlorophenyltetrahydrothiopyran-1-oxide (1.0 g, 0.004 mole), freshly

reduced copper (0.3 g, 0.005 mole), and p-toluenesulfonyl azide (3.0 g, 0.015 mole) were added to 60 ml of anhydrous methanol in a 250-ml three-necked flask and heated under reflux for 48 hours. After the dark green solution had cooled to room temperature, a slightly basic solution of ethylenediaminetetraaacetic acid (1.4 g, 0.0048 mole) was added dropwise. The product was obtained by the same procedure as above. The infrared spectrum and melting point (168-170° (lit.[35] mp 170-171°)) indicate that starting sulfoxide was recovered.

S,S-4-(p-Chlorophenyl)pentamethylene-N-p-toluenesulfonylsulfilimine (37) from cis-4-p-Chlorophenyltetrahydrothiopyran-1-oxide (36). p-Toluenesulfonamide (0.68 g, 0.0037 mole), triethylamine (1.5 g, 0.015 mole), and phosphorous pentoxide (0.9 g, 0.006 mole) in methylene chloride (50 ml) wereadded dropwise at 0° to cis-4-p-chlorophenyltetrahydrothiopyran-1-oxide (1.0 g, 0.0043 mole) which had been dissolved in methylene chloride. The reaction was stirred for 20 hours at 0° and two hours at room temperature. The methylene chloride solution was decanted and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the ethyl acetate was removed under reduced pressure until the liquid became cloudy. The solution, upon standing, yielded crystals. Recrystallization from acetone: petroleum ether (1:1) yielded

0.48 g (34.3%) of product, mp 214-215°.

Anal. Calcd for $C_{18}H_{20}ClNO_2S_2$: C, 56.60; H, 5.28; N, 3.67. Found: C, 57.12, H, 5.25; N, 3.63.

S,S-4-(p-Chlorophenyl)pentamethylene-N-p-toluenesulfonylsulfilimine (36) from 4-(p-Chlorophenyl)thiane.[36] 4-(p-Chlorophenyl)thiane (8 g, 0.04 mole) and chloramine T (12.1 g, 0.0534 mole) were dissolved in dioxane:water (2:1). After the solution was heated on a steam cone for two hours, the solvent was removed under reduced pressure. The resulting solid was dissolved in chloroform. The solution was washed three times with potassium hydroxide (10%) and several times with water. After removal of the chloroform, the crude sulfilimine was recrystallized from chloroform-ethyl acetate (1:1) until a constant mp of 213-214° was obtained.

S,S-4-(p-Chlorophenyl)pentamethylene-N-p-toluenesulfonylsulfoximine (38) from S,S-4-(p-Chlorophenyl)pentamethylene-N-p-toluenesulfonylsulfilimine (37).[36] S,S-4-(p-Chlorophenyl)pentamethylene-N-p-toluenesulfonylsulfilimine (3.0 g, 0.0079 mole), a large excess of potassium permanganate and 35 ml of pyridine were stirred at room temperature for three days. The reaction mixture was decolorized with sodium bisulfite and extracted with chloroform. The extracts were washed with water and evaporated to dryness. After recrystallization from petroleum ether:ethyl acetate, the melting point of the sulfoximine was 183-184°. The sulfoximine structure

was supported by infrared spectroscopy.

Anal. Calcd for $C_{18}H_{20}ClNO_3S_2$: C, 54.3; H, 5.06. Found: C, 56.1; H, 5.01.

Purification of S,S-4-(p-Chlorophenyl)pentamethylene-N-p-toluenesulfonylsulfoximine (38). The sulfoximine obtained above was recrystallized three times from petroleum ether:ethyl acetage (1:1). The product was obtained as white crystals (mp 188-188.5°).

Anal. Calcd for $C_{18}H_{20}ClNO_3S_2$: C, 54.33; H, 5.06; N, 3.52. Found: C, 54.43; H, 5.06; N, 3.69.

Copper Catalyst. Copper sulfate ($CuSO_4 \cdot 5H_2O$, 100 g, 0.404 mole) was dissolved in hot water (350 ml) and cooled to room temperature. Zinc dust (35 g, 0.53 g-atom) was added gradually until the solution was clear. After the precipitated copper was washed by decantation with water, dilute hydrochloric acid (5%) was added to remove excess zinc. The solution was stirred until the escape of hydrogen ceased. The copper powder was filtered, washed with water, and stored in a moist condition in a tightly stoppered bottle.

p-Toluenesulfonyl Azide. Sodium azide (44 g, 0.68 mole) was dissolved in water (100 ml) and mixed with 95% ethanol (180 ml). The mixture was cooled in an ice-salt bath. p-Toluenesulfonyl chloride (95.0 g, 0.50 mole), dissolved in 95% ethanol (450 ml) and water (100 ml), was added slowly to

the stirred, cold sodium azide solution. The mixture was stirred for two hours in the salt bath and two hours at room temperature. After the mixture was transferred to a separatory funnel, water was added until a white oil separated. The oil was diluted with ether, washed three times with water, and dried over anhydrous sodium sulfate. After removal of the sodium sulfate by filtration, the ether was distilled under reduced pressure at a temperature of 50°. (An explosion may occur if the temperature exceeds 50°.) The remaining white oil was then placed in a Dry Ice-acetone bath until white crystals formed. The solvent was decanted and the crystals, which became liquid at room temperature, were recrystallized from ether:petroleum ether (1:1). Infrared bands at 2120 cm^{-1} (N_3), 1305 cm^{-1} (N_3) and 1170 cm^{-1} (SO_2-N) indicated the presence of the sulfonyl azide.

SUMMARY

Optically active sulfoxides of known configuration were converted to sulfoximines under the conditions of the Kwart-Kahn reaction: methanol heated to reflux, aryl sulfonyl azide, copper and sulfoxide. The reaction produced optically active sulfoximines, whose absolute configurations were established by relating them to optically active sulfilimines of known configuration. The ORD, CD, and uv spectra of the optically active sulfoximines were taken. The levorotatory sulfoximines of the (R) configuration show a (-) Cotton effect at about 230 mμ. The work establishes some useful correlations among optically active sulfoxides, sulfilimines and sulfoximines.

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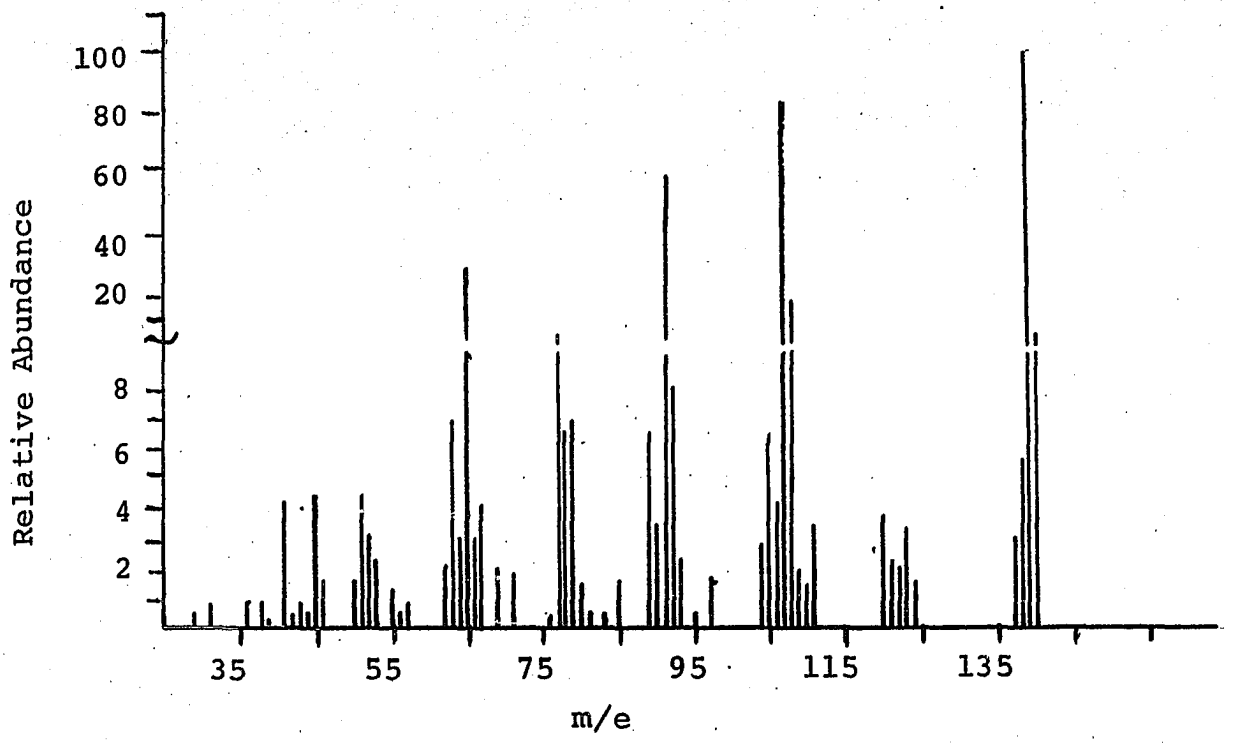
APPENDIX



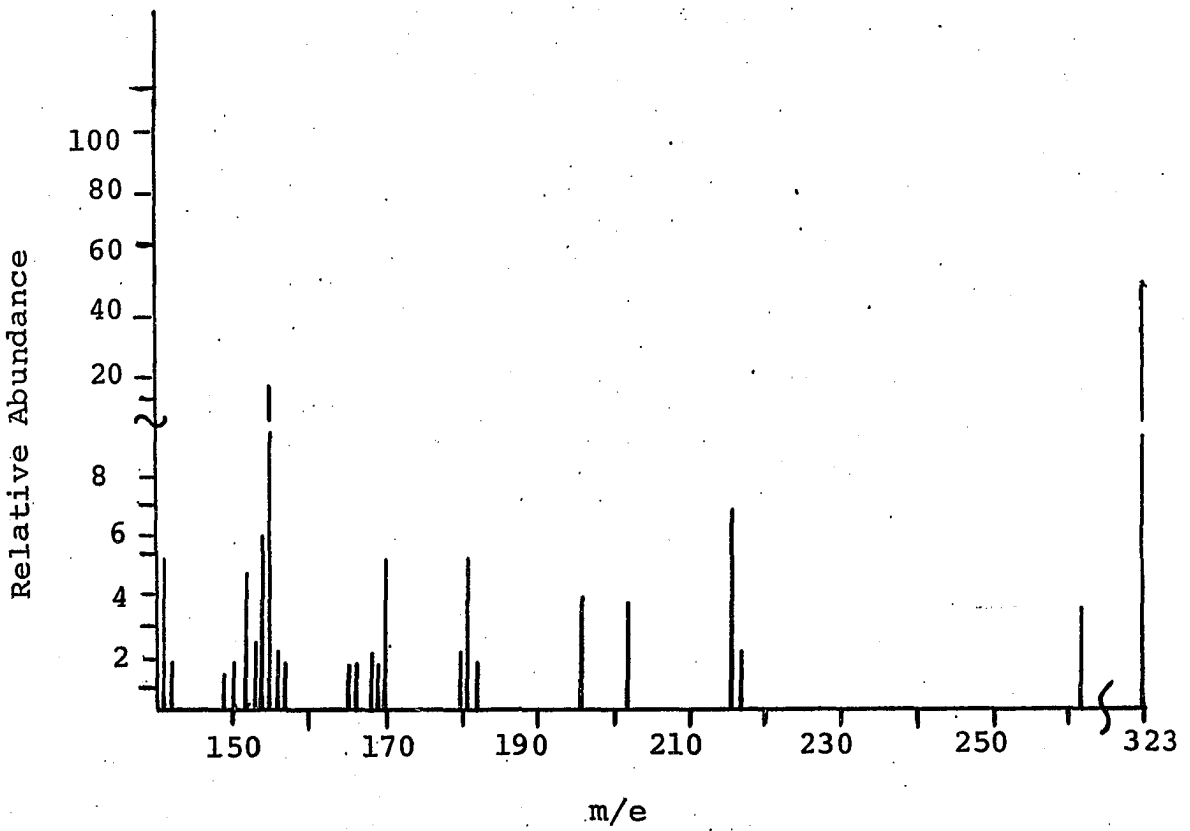


Figure H. Mass Spectral Data for (R)-S-Methyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine

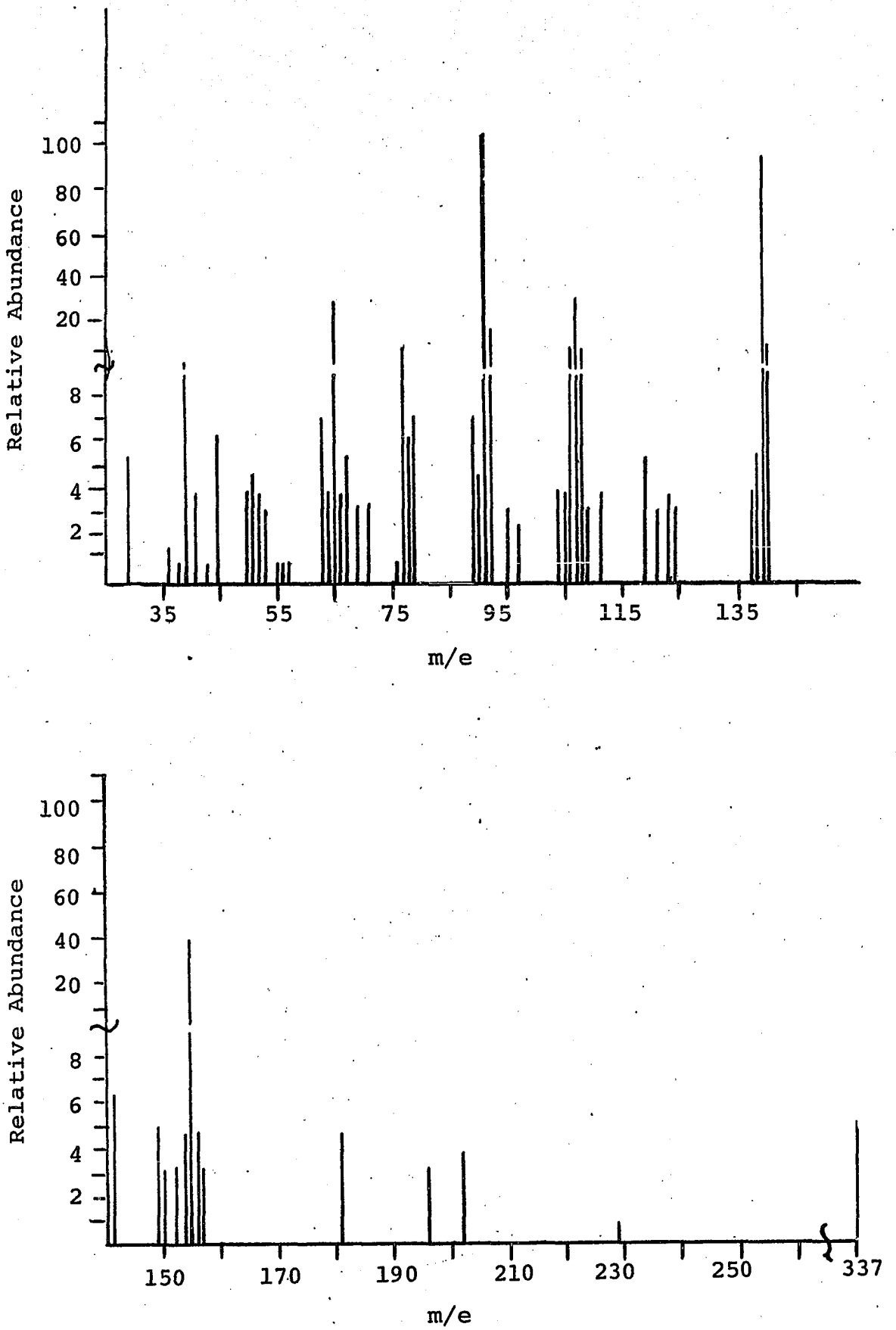


Figure I. Mass Spectral Data for (R)-S-Ethyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine

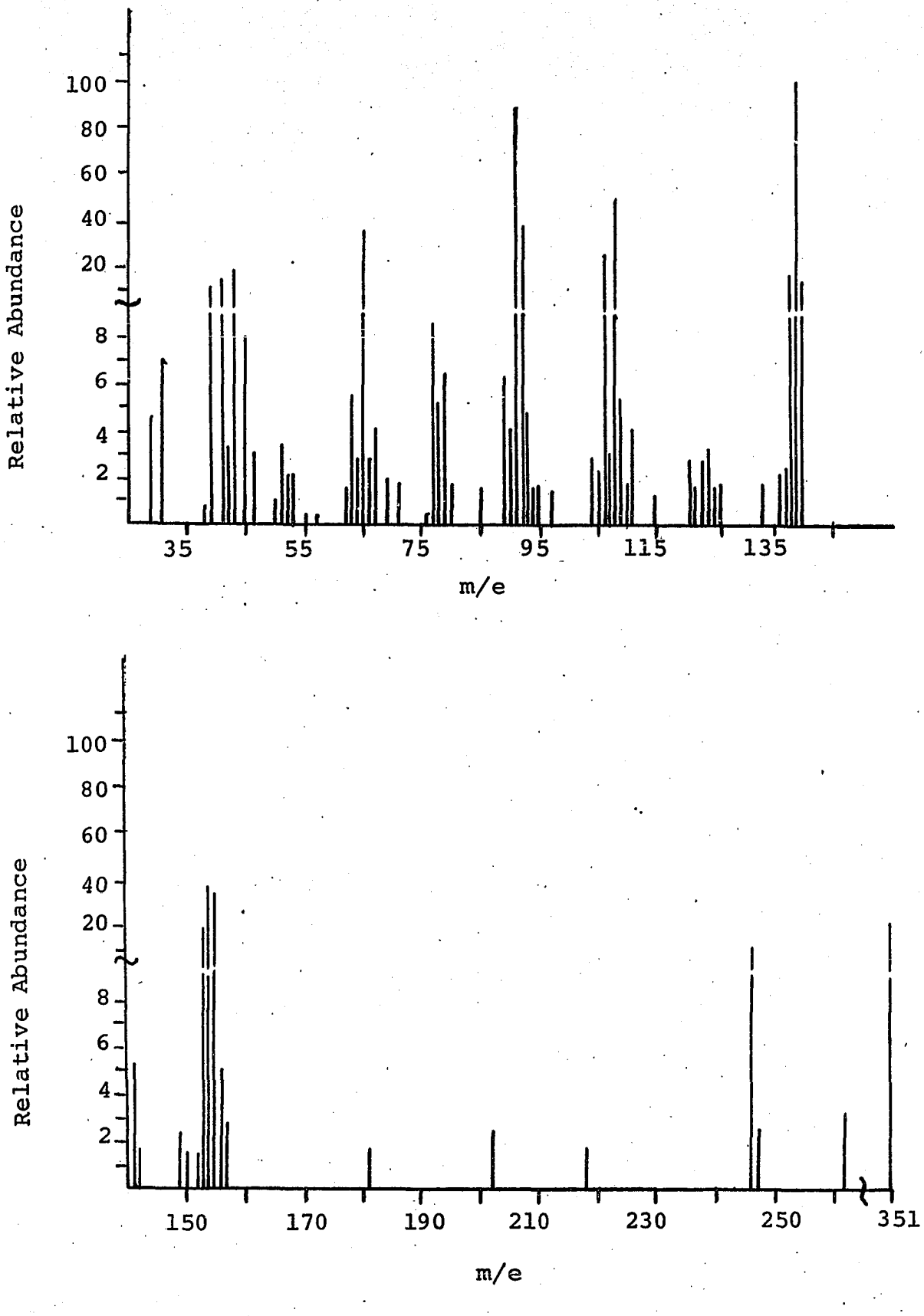


Figure J. Mass Spectral Data for (R)-S-Isopropyl-S-p-tolyl-N-p-toluenesulfonylsulfoximine

PART TWO

INTRODUCTION

The reaction of organometallic reagents with tetravalent sulfur compounds can lead to a variety of products.[1,2] The possible reactions for sulfates and sulfonate esters are shown in the following equations.

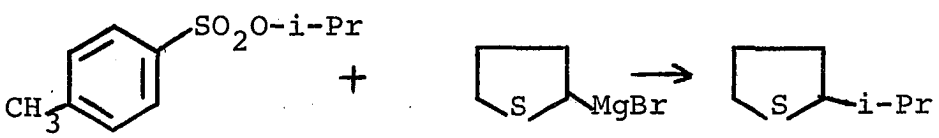
$$R'OSO_2OR' + RMgX \longrightarrow RH + R'(-H) + R'OSO_2OMgX \quad (1)$$

$$ArSO_2OR + R'MgX \longrightarrow RR' + ArSO_2OMgX \quad (2)$$

$$ArSO_2OR + R'MgX \longrightarrow RX + ArSO_2OMgR' \quad (3)$$

$$RSO_2OR' + R''MgX \longrightarrow RSO_2R'' + R'OMgX \quad (4)$$

The reaction product is determined to a large extent by the nature of the ester groups. The reaction of alkyl esters of aryl sulfonic acids with Grignard reagents proceeds according to equations (2) or (3). Thus, Hornfeldt and Gronowitz[3] reported that the reaction of isopropyl p-toluenesulfinate (1) with 2-thienylmagnesium bromide (2) resulted in the formation of 2-isopropylthiophene (3) (eq 5).

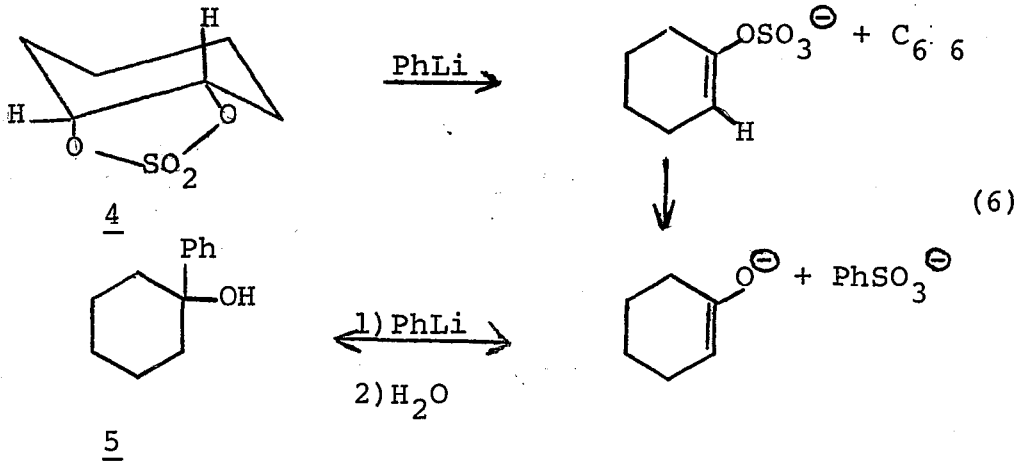


(5)

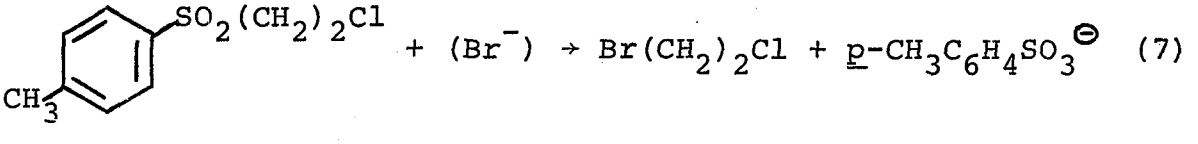
1 2 3

In the presence of phenyllithium, cis-1,2-cyclopentylene sulfate (4) gave 1-phenylcyclopentanol (5) (eq 6).[2] The

organometallic compound acted as a base, abstracting a β-hydrogen in an elimination reaction. A 3:1 ratio of organometallic reagent:sulfate was required in the reaction.



As shown by Johnson, Schwartz and Jacobus,[4] alkyl esters of aryl sulfonic acids with Grignards can also follow equation (3) (eq 7). Presumably the halide ion of the magnesium halide is the nucleophile.



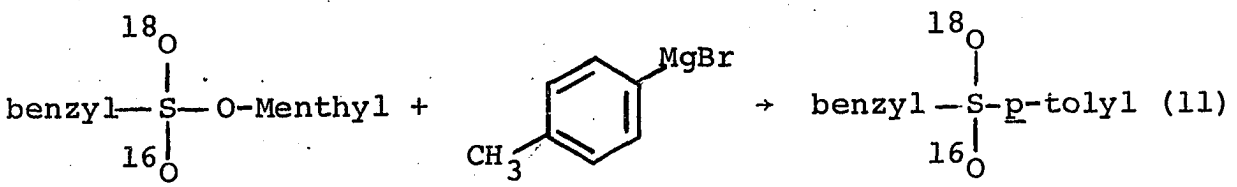
Although esters of alkyl sulfonic acids with Grignard reagents have been reported[5] to yield hydrocarbons (eq 8), another common reaction path for esters of alkyl sulfonic acids,[6] as well as for aryl esters of aryl sulfonic acids,[7] with Grignard reagents results in the formation of sulfones (eq 9 and eq 10).

$$(CH_2)_5CHSO_3C_2H_5 + C_6H_5MgBr \longrightarrow C_2H_5\text{-}C_6H_5 \quad (8)$$

$$C_2H_5SO_3C_2H_5 + C_6H_5MgBr \longrightarrow C_2H_5\text{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{-}C_6H_5 \quad (9)$$

$$C_7H_7SO_3C_6H_5 + C_7H_7MgBr \longrightarrow C_7H_7\text{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{-}C_7H_7 \quad (10)$$

This part of the Thesis is concerned with an investigation of the stereochemical course of the reaction of an alkyl ester of an alkyl sulfonic acid with a Grignard reagent to produce a sulfone. The reaction can be studied by the use of ^{18}O labeled sulfonate (6). The specific reaction under investigation is shown below (eq 11).



(11)

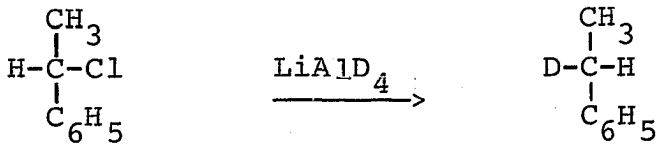
6 7

If the benzyl p-tolyl sulfone (7) obtained is not optically active, the reaction can be said to proceed by racemization. If, however, an optically active sulfone is obtained, it can be stated whether the reaction proceeds with predominant inversion or retention of configuration since the absolute configuration of sulfone 7 has been reported.[8]

More generally, the purpose of the investigation was to determine the stereochemical consequence of a nucleophilic substitution on a tetracoordinate sulfur system. To date, virtually no stereochemical studies have been carried out for nucleophilic attack at tetracoordinate sulfur.

RESULTS AND DISCUSSION

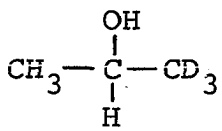
The existence of compounds of the type Caa'bc, whose optical activity can be attributed to the presence of two different isotopes (a and a') of an element on the same carbon, has been well substantiated in the literature. Eliel[9] has isolated an optically active deuterium hydrocarbon (1), $[\alpha]_D$ +0.30°, from the reduction of an optically active alkyl chloride, $[\alpha]_D$ -49.2° (eq 1).



(1)

1

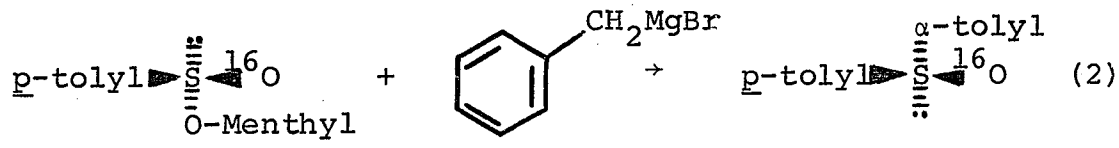
Chiral compounds in which the isotope is on a carbon one atom removed from the center of asymmetry have also been reported. Thus, Mislow and coworkers[10] have shown compound 2 to have $[\alpha]_D$ +0.27°.



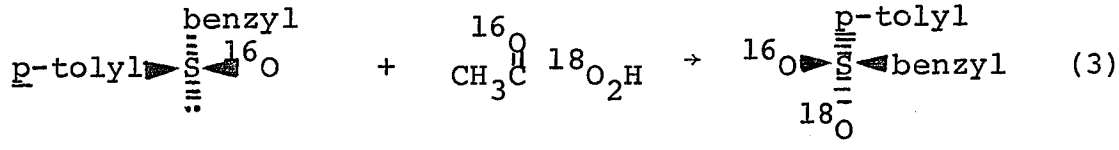
2

In recent years countless examples of optical activity due to an isotope of hydrogen (either deuterium or tritium) have been reported.[11,12] However, only one case of asymmetry caused by an isotope of oxygen has been reported. In this one instance[8] the center of asymmetry was a sulfur, rather than a carbon, atom.

(+)-Benzyl p-tolyl sulfoxide (4), prepared[8] by the reaction of benzyl Grignard reagent with (-)-menthyl p-toluenesulfinate (3) (eq 2), was oxidized (eq 3) with labeled peroxyacetic acid to yield an optically active sulfone (5), $[\alpha]_D$ -0.16°.



3 4 (2)

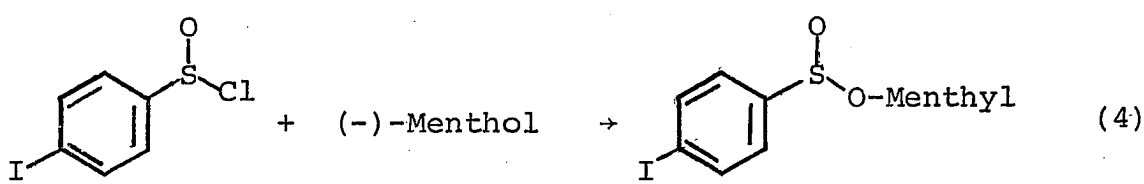


4 5 (3)

Three assumptions were involved in assigning 5 the (S) configuration: (a) the (-)-menthyl (-)-p-toluenesulfinate (4a) has the (S) configuration; (b) the Grignard reaction leading from the ester to the sulfoxide (eq 2) proceeded with inversion of configuration to yield sulfoxides of the (R)

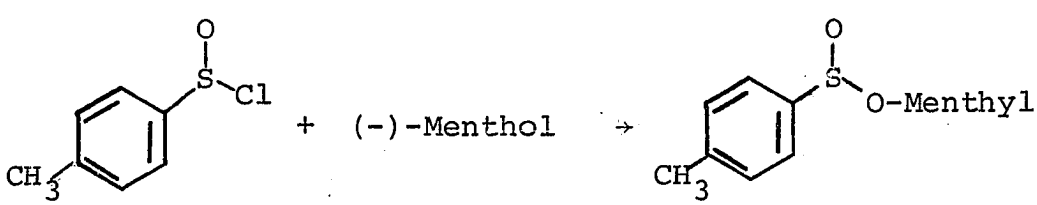
configuration; and (c) the oxidation of sulfoxide to sulfone (eq 3) proceeded with retention of configuration. Arguments involving the validity of these assumptions follow.

Mislow and coworkers[13] prepared a mixture (6) of diastereomeric (-)-menthyl p-iodobenzenesulfinyl chloride with (-)-menthol. Under the non-equilibrating conditions of the experiment, mixture 6 was found to contain 74.1% of the (+)-6 diastereomer. A diastereomeric mixture (7) of (-)-menthyl p-toluenesulfinates was then formed (eq 5) under the same reaction conditions as above. It was established[13] that mixture 7 contained 63.3% of the (+)-7 diastereomer.



(4)

6



(5)

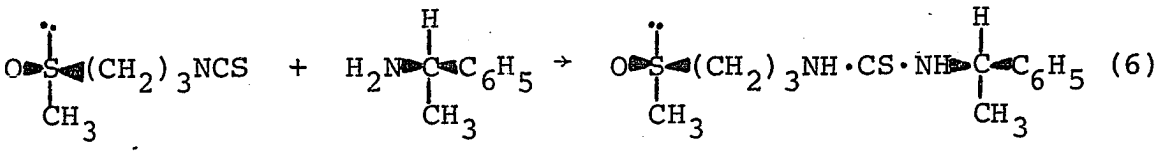
7

Since, under the non-equilibrating conditions of the reaction, (+)-6 and (+)-7 were found to be the kinetically controlled products, it was assumed that both had the same configuration. The absolute configuration of (-)-6 had been previously established[14] as (S) by X-ray methods. Therefore (+)-6 and (+)-7 can be said to have the (R) configuration.

It follows that (-)-menthyl (-)-p-toluenesulfinate ((-)-7) has the (S) configuration. Thus, assumption (a) (p 71) has been verified.

The most convincing argument in favor of inversion of configuration in the reaction of sulfinate esters with Grignard reactions (assumption (b), p 71) was presented by Mislow and coworkers.[15] (-)-Menthyl (-)-p-iodosulfinate (15) and (-)-iberin (8), two compounds whose absolute configurations have been determined by X-ray methods, were related by a series of reactions. The reaction sequence is presented in Scheme I.

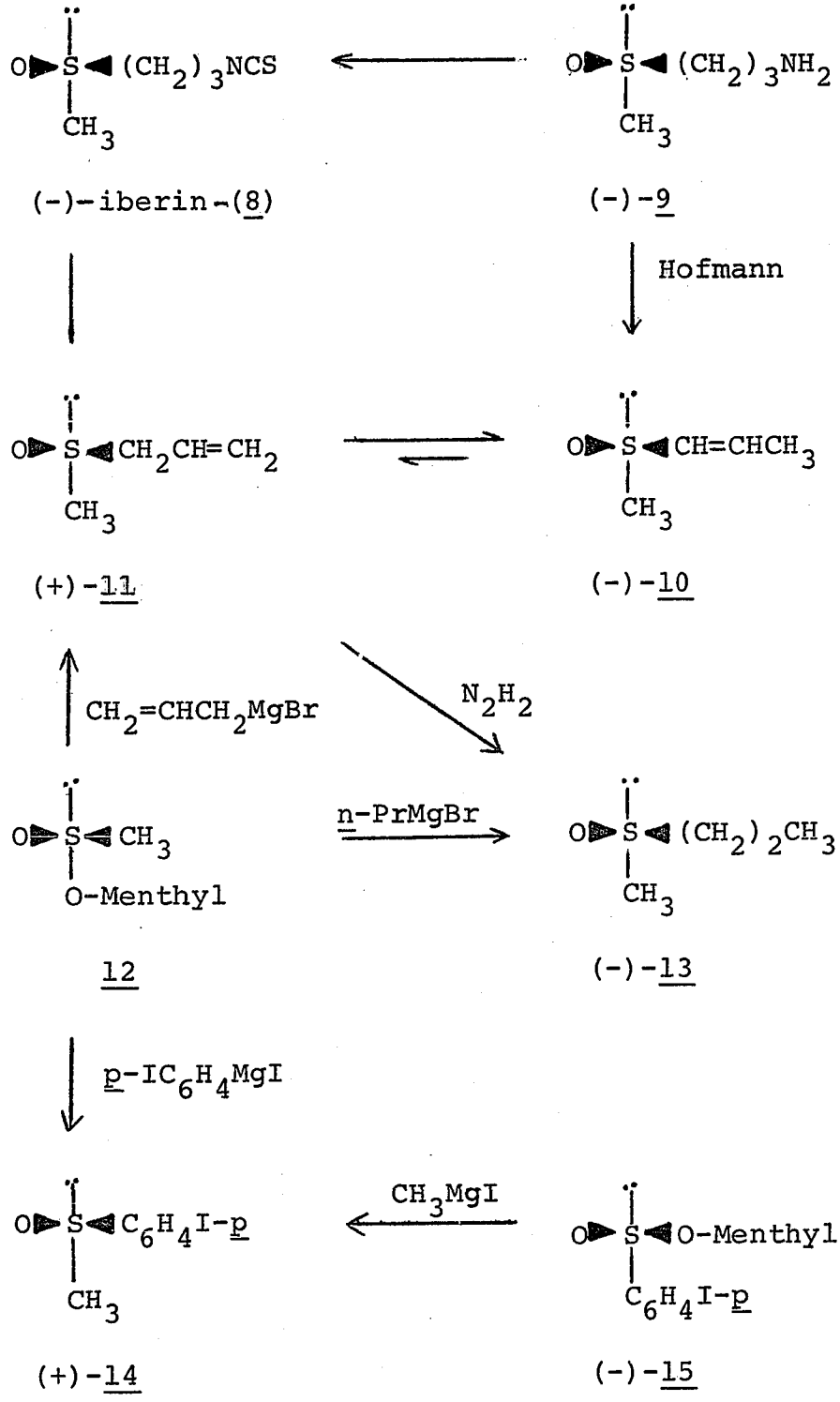
The absolute configuration of (-)-iberin (8) was established[16] through conversion of 8 into its thiourea derivative (17) by means of reaction with (+)-α-methylbenzylamine (16) (eq 6). The X-ray analysis of the thiourea derivative indicated that the absolute configuration around the sulfur atom was (R).



(6)

8 (+)-(R)-16 17

The absolute configuration around the sulfur atom in (-)-15 had previously been shown[14] by X-ray analysis to be (S).



SCHEME I

The absolute configuration of (-)-9 was established as (R) by conversion of this compound to (-)-iberin (8). Under the conditions of the Hofmann elimination (-)-9 yielded a product ($[\alpha]_D$ -142° (ethanol)) which was found to contain 20% of (+)-11 and 80% of (-)-10 by nmr. It is not expected that the stereochemistry of the sulfur atom would be affected during this Hofmann elimination, so the (R) configuration was established for both (+)-11 and (-)-10.

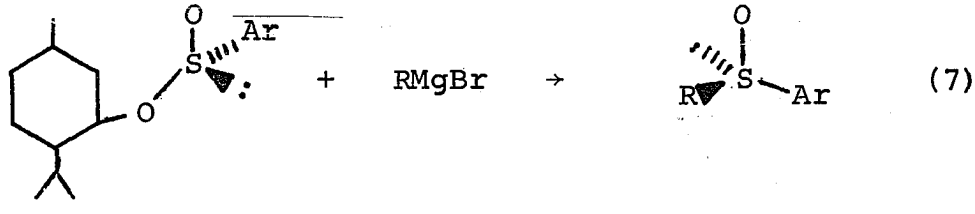
The diastereomeric purity of a mixture of (-)-menthyl methanesulfinates (12), presumably enriched in the (R)-epimer,[17] was determined by conversion of sulfoxides. It had been previously shown[13] that in the reaction of sulfinate esters with Grignard reagents, the ratio of enantiomers in the product sulfoxides reflected the ratio of diastereomers in the starting ester. Using this relationship, (12) was found to be 32.4% diastereomerically pure. Treatment of 12 with n-propylmagnesium bromide yielded (-)-methyl n-propyl sulfoxide (-)-13, $[\alpha]_D$ -42° (ethanol). Also, treatment of 12 with allylmagnesium bromide gave (+)-11, $[\alpha]_D$ +4.9° (ethanol). Reduction of (+)-11 with diimide yielded (-)-13, $[\alpha]_D$ -35° (ethanol). Since the configuration of (+)-11 had been established as (R) (above), the (R) configuration was assigned to (-)-13.

A similar mixture of 12, 29% diastereomerically pure, when treated with p-iodophenylmagnesium iodide, yielded (+)-methyl p-iodophenyl sulfoxide (14). Compound (+)-14 must have the same configuration as (-)-13 and (-)-11 since all arise from the same precursor. Thus, (+)-14 has the (R) configuration.

The only assumption made here is that the three Grignard reactions leading to 11, 13 and 14 have the same stereochemical paths.

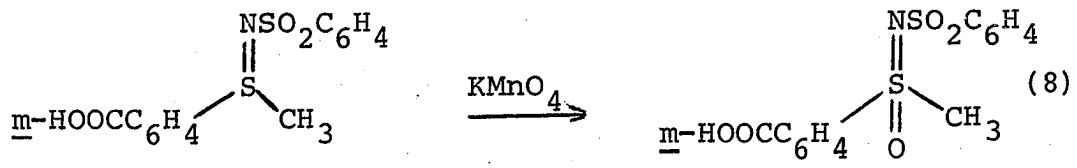
The reaction of methylmagnesium iodide with diastereomerically pure (-)-menthyl (-)-p-iodobenzenesulfinate ((-)-15) yielded (+)-14, $[\alpha]_D$ +99° (ethanol). Since the absolute configuration of (-)-15 has been shown[13] by X-ray to be (S) and the absolute configuration of (+)-14 has been shown by the above chemical transformations to be (R), the Grignard reaction converting (-)-(S)-15 to (+)-(R)-14 can be said to proceed with inversion.

The absolute configuration of optically active sulfoxides produced by the reaction of optically active sulfinate esters and Grignard reagents can now be assigned. It has been found that aryl sulfinate esters of a given configuration produce sulfoxides of the opposite configuration (eq 7). When the Grignard reagent is alkyl, the (S) sulfinate will yield the (R) sulfoxide. Thus, assumption (b) (p 71) has been verified.



(7)

Experimental evidence for the stereochemical course of oxidation at a trigonal sulfur atom (see assumption (c), p 72) has been presented by Kresze and Wustrow.[18]



(8)

18 19

In an attempt to establish the stereochemical course of equation (8), Kresze and Wustrow[18] employed ORD techniques and the Freudenberg Displacement Rule.[19] Under the conditions of the oxidation (eq 8), sulfilimine 18, $[\alpha]_D$ +254°, yielded the sulfoximine 19, $[\alpha]_D$ +143°. The ORD curves of both 18 and 19 are shown in Figure A. It would appear from the ORD curves in Figure A that 18 and 19 have the same configuration.

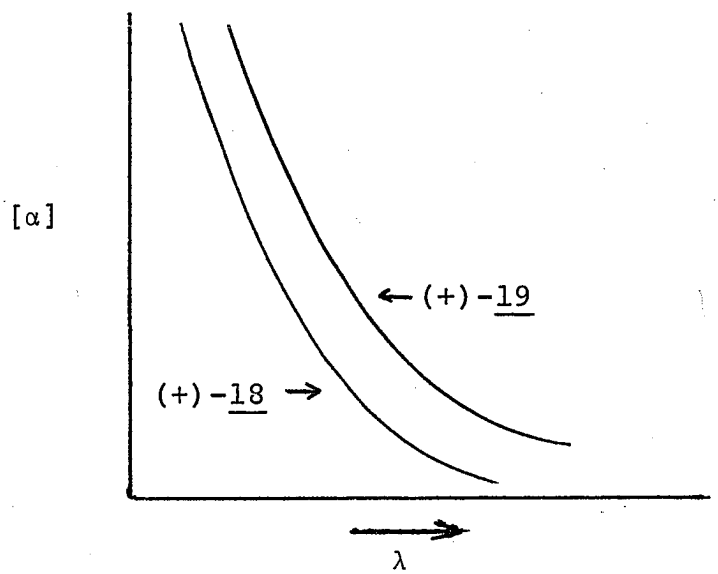


FIGURE A

Sulfilimine 18 and sulfoximine 19 were then converted to several derivatives. The derivatives and their D-line

rotations are shown in Table I.

	Sulfilimine $[\alpha]_D$ 18	Sulfoximine $[\alpha]_D$ 19
Acid	+254°	+143°
Na salt	+246°	+112°
Methyl ester	+243°	+133°
Amide	+259°	+149°

TABLE I

According to the Freudenberg Displacement Rule, "when similarly constituted dissymmetric compounds are chemically changed in the same way and the change produces a considerable shift in optical rotation in the same direction, then the two compounds probably have the same configuration."[20]

Since the D-line rotations of all the derivatives of 18 and 19 in Table I change considerably and in the same direction, sulfilimine 18 and sulfoximine 19 would appear to have the same configuration if the Freudenberg Displacement Rule can be applied to this system.

However, the above arguments in favor of similar configurations for 18 and 19 have a major weakness. Establishment of absolute configuration either by comparison of ORD curves or by the Freudenberg Displacement Rule requires that the two compounds being compared have similar structures at the asymmetric center. In the present case the structure of 18 involves asymmetry around a trivalent sulfur atom while 19 involves asymmetry around a tetravalent sulfur. The

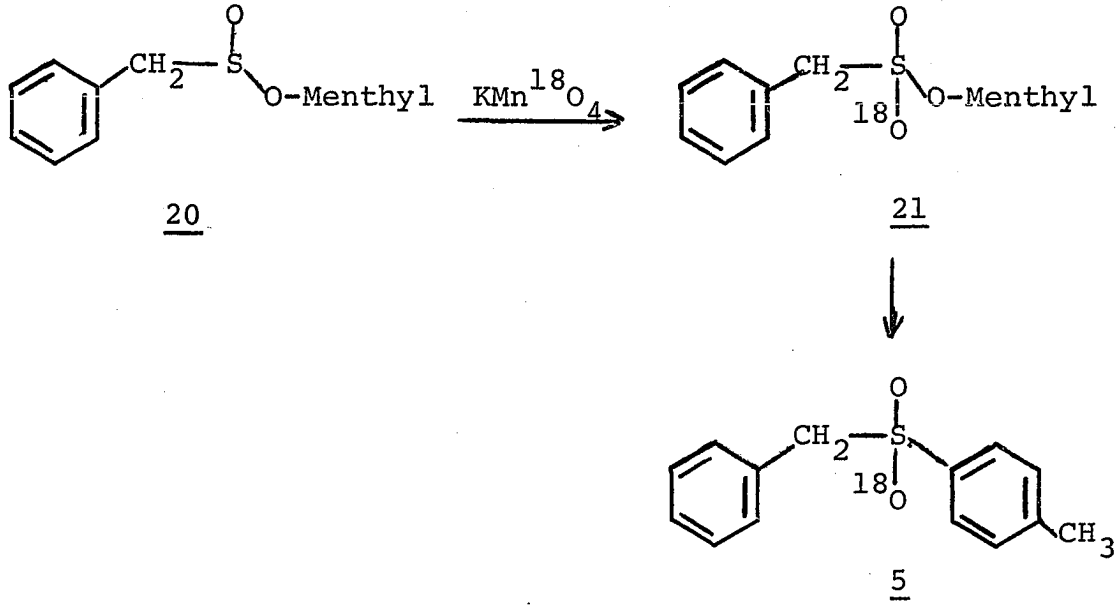
question is whether these structures can be considered similar enough to compare by these methods. To date this question has not been resolved.

The possibility remains that the relative configuration of 19 can be assigned validly from the configuration of 18 on the basis of both the similarity of the ORD curves and the Freudenberg Displacement Principle. If the arguments presented by Kresze and Wustrow[18] are accepted, 19 has the same configuration as 18 and it can be said that the oxidation (eq 8) proceeds with retention.

It should be made clear that the above arguments should not be accepted as rigorous proof that the oxidation of a trivalent sulfur compound to a tetravalent sulfur compound proceeds with retention; even Kresze and Wustrow point out the shortcomings of these arguments. The arguments, however, do lend some support to the hypothesis that the oxidation occurs with retention. Thus, these arguments support assumption (c) (p 72).

Substantial proof has now been presented that the absolute configuration of (-)-menthyl p-toluenesulfinate has the (S) configuration (p 71) and that the reaction of Grignard reagents with sulfinate esters proceeds with inversion (p 71). Arguments have also been presented which support the premise of retention of configuration in the oxidation reaction of trivalent sulfur compounds to tetravalent sulfur compounds (p 72). Therefore it can be concluded that the assignment (p 71) of the (S) configuration for benzyl p-tolyl sulfone ((-)-5) is valid.

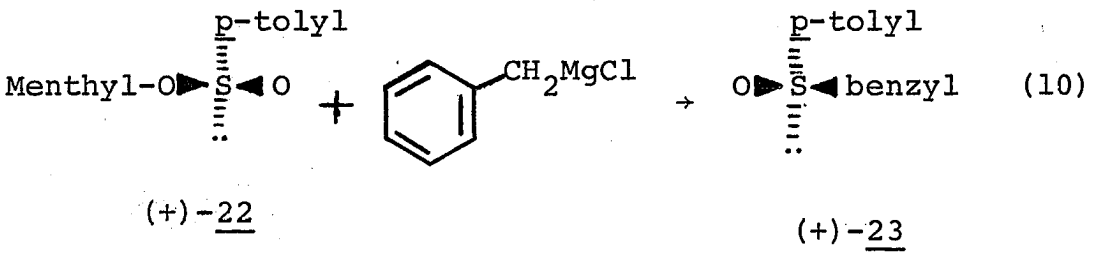
Once the absolute configuration of ^{18}O labeled sulfone had been established, the stereochemical course of the reaction of sulfonate esters with Grignards leading to sulfones could be investigated. The specific reaction sequence that was employed is shown in Scheme II.



20 21 5

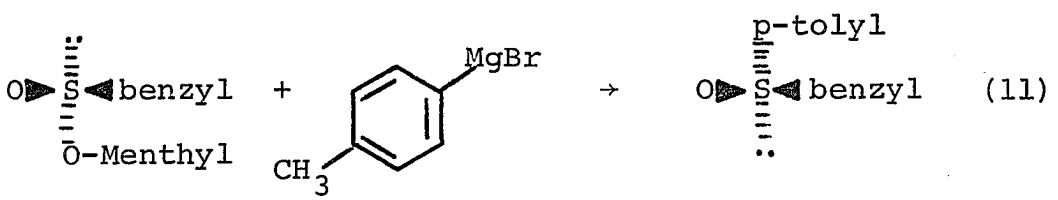
SCHEME II

The absolute configuration of (+)-20 was established in the following way. (S)-(-)-Menthyl (-)-p-toluenesulfinate (22) was treated[8] with benzyl magnesium chloride to yield a dextrorotatory sulfoxide (23) (eq 10). It has been shown (p 71) that (-)-22 has the (S) configuration and that the reaction of sulfinate esters with Grignard reagents proceeds with inversion (p 71). Therefore, sulfoxide (+)-23 must have the (R) configuration.



(+)-22 (+)-23 (10)

The same sulfoxide (+)-23 was obtained[21] in the reaction of (-)-menthyl α-toluenesulfinate (+)-20 with p-tolylmagnesium bromide (eq 11).

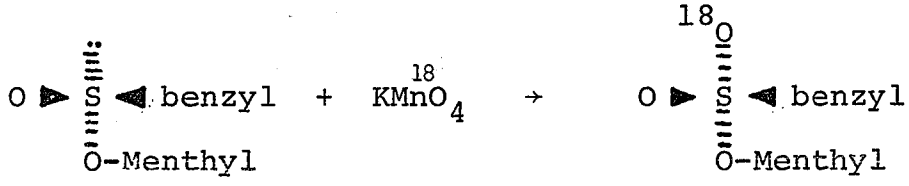


(+)-20 (+)-23 (11)

Since (+)-23 had been assigned the (R) configuration (p 80) and the reaction of Grignards with sulfinate esters had been established as proceeding with inversion (p 71), it can be concluded that (+)-20 has the (R) configuration.

Initially, the oxidation of sulfinate 20 to sulfonate 21 (Scheme II) was to be achieved using ^{18}O labeled peroxyacetic acid. The labeled peroxyacetic acid was to be made by the reaction in a vacuum system of normal acetic acid with

labeled sodium peroxide ($Na_2{}^{18}O_2$). A vacuum line was built (see experimental section) to achieve the preparation of the labeled peracid, but it was decided that using commercially available ^{18}O potassium permanganate as an oxidant would be more economical and less time-consuming. Therefore the conversion of 20 to 21 (eq 12) was accomplished with the labeled permanganate. Since there is evidence that oxidation at trigonal sulfur proceeds with retention of configuration (p 72), sulfonate 21 was assigned the (R) configuration.



(R)-20 (S)-21

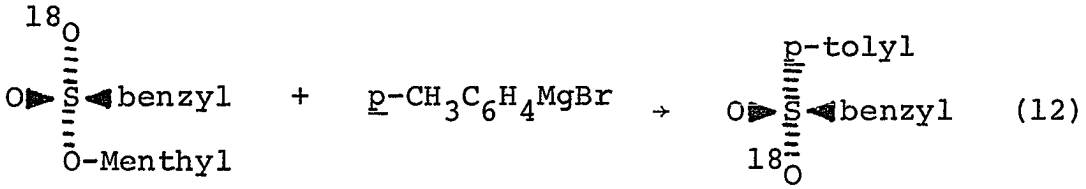
When sulfonate 21 was treated with p-tolylmagnesium bromide, ^{18}O-benzyl p-tolyl sulfone (22) was obtained. The following tests were carried out to show that the sulfone was not contaminated by optically active (-)-menthol or optically active benzyl p-tolyl sulfoxide. The latter could form by the reaction of unoxidized (-)-menthyl α-toluenesulfinate (20) with p-tolylmagnesium bromide.

Unlabeled benzyl p-tolyl sulfone was contaminated with (-)-menthol. The mixture was extracted with boiling petroleum

ether to remove the (-)-menthol. The ORD curve of the remaining sulfone indicated that the (-)-menthol had been effectively removed.

Optically active benzyl p-tolyl sulfoxide was then mixed with unlabeled benzyl p-tolyl sulfone, and both were dissolved in glacial acetic acid. The sulfoxide was then reduced to the sulfide with titanium(III) chloride. After the sulfide was removed by extraction with petroleum ether, the ORD curve of the recovered sulfone was taken. The dispersion curve showed that the sulfoxide had been eliminated.

The ^{18}O-benzyl p-tolyl sulfone was purified by the above reactions to remove (-)-menthol and (+)-benzyl p-tolyl sulfoxide. The ORD curve of the sulfone showed a negative plain curve. Since Stirling[6] assigned the (S) configuration to the levorotatory ^{18}O-benzyl p-tolyl sulfone, the (S) configuration was assigned to 22 (eq 12).



(12)

(S)-21 (S)-22

To insure that the negative plain curve was not due solely to (-)-menthol, the dispersion curve of (-)-menthol

was taken and compared with the curve of the ^{18}O-sulfone. It can be seen (Figure B' in Appendix) that the curves do not have similar slopes. The slope of the sulfone's dispersion curve is more pronounced than that of the (-)-menthol curve as shorter wavelengths are approached; the optical activity of the sulfone cannot be due to traces of (-)-menthol alone (blank experiments have ruled this out previously), and we conclude that the sulfone caused the levorotation. From this evidence levorotatory ^{18}O-sulfone can be assigned the (S) configuration. Therefore, the reaction of (-)-menthyl α-toluenesulfonate with p-tolylmagnesium bromide proceeded with inversion of configuration.

EXPERIMENTAL

Peroxyacetic Acid.[22] Sodium peroxide was prepared at a pressure of 1×10^{-4} mm. A 100-ml Pyrex three-necked flask was heated to 260°. A film of sodium was thrown on the internal surface of the bulb by electrically heating a tungsten spiral which contained a piece of sodium. After the film of sodium was on the bulb, oxygen gas, contained in a 100-ml flask, was allowed to diffuse into the bulb. The reaction flask was kept at 260° for one hour and then cooled to -20°. A mixture of acetic acid (7 ml) and water (3 ml) was cooled to -20° and slowly added to the reaction mixture. (The low temperatures were used to prevent a fire on contact of aqueous acetic acid and peroxide.) A 1-ml aliquot of the mixture was treated with an excess of aqueous potassium iodide and a trace of ammonium molybdate. The liberated iodine was treated with 0.05 N sodium thiosulfate. Starch was used as an indicator. The yield of peroxyacetic acid was 9%.

α-Toluenesulfonyl Chloride. A slow stream of anhydrous sulfur dioxide was directed at the surface of an ethereal solution of α-tolylmagnesium chloride, prepared from α-chlorotoluene (126 g, 113 ml, 1.00 mole), magnesium (28.0 g, 1.22 mole), and 450 ml of anhydrous ether. A solid film formed, which was broken up repeatedly by stirring. After all of the solvent evaporated (4 hr), ether was added to the solid residue,

and a stream of chlorine gas was bubbled into the suspension for about three hours. Water was slowly added to the mixture until two layers formed. The dark red oil which separated was diluted with chloroform and dried over anhydrous magnesium sulfate. After filtration of the solution and removal of solvent, a brown oil remained which yielded yellow-brown crystals. After recrystallization from chloroform, the product (26.2 g, 13.8% based on α-chlorotoluene) was obtained as white crystals, mp 90.5-91.5° (lit.[23] mp 90-92°).

(-)-Menthyl α-Toluenesulfonate. α-Toluenesulfonyl chloride (25 g, 0.13 mole) and (-)-menthol (20 g, 0.13 mole) were dissolved in anhydrous ether and cooled in an ice-salt bath. Anhydrous pyridine (20 g, 0.25 mole, 21 ml) in anhydrous ether was added dropwise over a 4.5-hr period. After the white, crystalline pyridine hydrochloride was removed by filtration, the solvent was removed under reduced pressure. An orange oil remained which crystallized on standing. The product (26 g, 59%) was obtained as white crystals, mp 64-65.5° (lit.[24] mp 66-67°).

α-Toluenesulfinyl Chloride. Chlorine gas (22.0 g, 0.300 mole) was added to a mixture of benzyl disulfide (24.8 g, 0.100 mole), glacial acetic acid (11.4 ml, 0.200 mole) and freshly distilled methylene chloride (80 ml) at -40°. After the orange solution had come to room temperature, nitrogen gas was bubbled through the liquid for several hours. The solution

was heated to 70° and cooled. Acetyl chloride was removed by distillation at an aspirator pressure of 14 mm and a pot temperature of 30°. A Dry Ice-acetone trap was inserted between the system and the aspirator to prevent escape of the acetyl chloride. When condensation of acetyl chloride ceased, the residual sulfinyl chloride was stoppered and refrigerated. The liquid showed a strong infrared absorption at 1158 cm^{-1}, indicating[25] the presence of sulfinyl chloride.

(-)-Menthyl α-Toluenesulfinate. (-)-Menthol (31 g, 0.20 mole) was dissolved in anhydrous ether; the resulting solution was mixed with anhydrous pyridine (15 ml) and cooled to 0°. The above α-toluenesulfinyl chloride was diluted with anhydrous ether, cooled to -40°, and slowly added to the chilled (-)-menthol and pyridine. Anhydrous ether was added to the resulting thick pink paste, and stirring was continued for one hour at 0°. Extraction at 0° with a solution of sodium carbonate (5%), water, a solution of hydrochloric acid (1%), and water, in that order, yielded a bright orange ether layer which was dried over anhydrous magnesium sulfate. After filtration of the solution and evaporation of most of the ether, the remaining solution yielded crystals which were recrystallized from ethanol yielding 8.80 g (64.5%) of product, mp 72-75°, $[\alpha]_D$ +105° (c 2.0 chloroform), (lit.[20] $[\alpha]_D$ +105° (chloroform)).

(-)-Menthyl α-Toluenesulfonate from (-)-Menthyl α-Toluenesulfinate. (-)-Menthyl α-toluenesulfinate (0.934 g, 0.00316 mole) was dissolved in a minimum amount of acetone and added dropwise at room temperature to a solution of 0.500 g (0.00316 mole) of potassium permanganate in 40 ml of acetone. The mixture was stirred for two days, the reaction mixture was centrifuged, and the clear liquid decanted. The manganese dioxide was washed with acetone and centrifuged and all of the decanted liquids were combined. The solvent was removed under reduced pressure. The crystals that were obtained from the remaining yellow oil were dissolved in a minimum amount of chloroform and chromatographed on a column (32 cam long, 3.0 cm diameter) of silica gel (Fisher, Powder) using spectral grade chloroform as eluent. The product (0.435 g, 45.5%) was collected as white crystals, mp 64-65.5° (lit.[25] mp 66-67°).

^{18}O-(-)-Menthyl α-Toluenesulfonate from ^{18}O-(-)-Menthyl α-Toluenesulfinate. The procedure was the same as that used for the oxidation of the ^{16}O-(-)-menthyl α-toluenesulfinate (above). Using exactly the same quantities as above,[26] a 44.5% yield of ^{18}O-(-)-menthyl α-toluenesulfonate, mp 64.5-66° (lit.[25] mp for ^{16}O analogue 66-67°), was obtained.

Benzyl p-Tolyl Sulfone. The Grignard reagent prepared from p-bromotoluene (5.3 g, 0.031 mole) and oven-dried magnesium

turnings (0.75 g, 0.031 mole) in anhydrous ether (50 ml) was titrated with 1.00 N sec-butyl alcohol in xylene using 1,10-phenanthroline as an indicator. The solution was found to contain 0.0006 mole of Grignard reagent per ml.

The Grignard reagent (5.0 ml, 0.0031 mole) was added over a period of ten minutes to a solution of (-)-menthyl α-toluenesulfonate (0.96 g, 0.0031 mole) which had been heated to reflux. The addition was carried out under a slow stream of sulfuric acid-dried nitrogen. After stirring at reflux for 1.5 hr, the mixture was cooled to 0° and hydrolyzed with a saturated solution of ammonium chloride. The salts were removed by filtration and washed with ether. The combined ether layers were dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the ether was evaporated under reduced pressure. The remaining oil crystallized. The product (0.14 g, 18%) was recrystallized from benzene: alcohol (1:1), mp 140-142° (lit.[6] mp 143.5-145°).

Mass Spectral Data: see Figure A' in Appendix.

^{18}O-Benzyl p-Tolyl Sulfone. The Grignard reagent prepared from p-bromotoluene (5.3 g, 0.031 mole) and oven-dried magnesium turnings (0.75 g, 0.031 mole) in anhydrous ether (50 ml) was titrated with 1.00 N sec-butyl alcohol in xylene using 1,10-phenanthroline as an indicator. The solution was found to contain 0.0006 mole of Grignard reagent per ml. The Grignard reagent (0.039 g, 0.0018 mole, 2.0 ml) was added over a period of five minutes to a solution of (-)-menthyl α-toluenesulfonate (0.43 g, 0.0014 mole), which had been heated to reflux. The

addition was carried out under a slow stream of sulfuric acid-dried nitrogen. After stirring at reflux for 1.5 hr, the mixture was cooled to 0° and hydrolyzed with a saturated solution of ammonium chloride. The salts were removed by filtration and washed with ether. The combined ether layers were dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the ether was evaporated under reduced pressure. The remaining white solid was dissolved in a minimum amount of spectral grade chloroform and chromatographed on a column (32 cm long, 3.0 cm diameter) of silica gel (Fisher, Powder) using spectral grade chloroform as eluent. The product (0.067 g, 15%) was collected as white crystals, mp 143-145° (lit.[6] mp for unlabeled sulfone 143.5-145°).

Removal of (-)-Menthol from ^{16}O-Benzyl p-Tolyl Sulfone.[6] (-)-Menthol (9.2 mg, 0.059 mmole) and ^{16}O-benzyl p-tolyl sulfone (49 mg, 0.20 mmole) were dissolved in chloroform. After removal of the chloroform, (-)-menthol was removed from the mixture by two 20-ml extractions with boiling petroleum ether (bp 30-65°). The ORD curve of the remaining benzyl p-tolyl sulfone showed $[\alpha]_{320}$ -0.0003° ± 0.0002° (c 1.5, chloroform).

Removal of Benzyl p-Tolyl Sulfoxide from ^{16}O-Benzyl p-Tolyl Sulfone.[6] (+)-Benzyl p-tolyl sulfoxide (1.0 mg, 0.41 mmole), $[\alpha]_D$ +244° (lit.[6] $[\alpha]_D$ +252°)), inactive benzyl p-tolyl sulfone (35 mg, 0.14 mmole), and sodium acetate (930 mg, 1.10 mmole) were dissolved in glacial acetic acid (4.5 ml) and the mixture was diluted with water (1.8 ml). After addition of a

20% solution of titanium(III) chloride (200 mg, 1.80 mmole, 1.0 ml), the reaction mixture was heated (hot water bath) for three hours at 70°. The reaction mixture was cooled to room temperature and extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the chloroform was removed under reduced pressure. The residue was washed with petroleum ether (35-60°) to remove benzyl p-tolyl sulfide. The product (0.015 g, 43%) was obtained as white crystals (mp 143-145° (lit.[6] mp 145.5-145°); $[\alpha]_{320}$ -0.0018 ± 0.0002° (c 1.5, chloroform)).

Removal of (-)-Menthol and Benzyl p-Tolyl Sulfoxide from ^{18}O-Benzyl p-Tolyl Sulfone. ^{18}O-Benzyl p-tolyl sulfone (37.8 mg, 0.153 mmole) was boiled in petroleum ether as above to remove any (-)-menthol that might have been present. The recovered ^{18}O-benzyl p-tolyl sulfone (29.6 mg, 0.120 mmole) was treated with titanium(III) chloride as above to remove any (+)-benzyl p-tolyl sulfoxide that might have been present. The product, mp 141-143° (lit.[6] mp 143.5-145°) had $[\alpha]_{320}$ -1.55° (c 1.3, chloroform).

Mass Spectral Data: see Figure B' in Appendix.

ORD Data: see Figure C' in Appendix.

SUMMARY

The stereochemical course of the reaction of an alkyl sulfonate ester with an aryl Grignard reagent was established. Isotopic ^{18}O-(-)-menthyl p-toluenesulfonate was prepared by the oxidation of the corresponding sulfinate with ^{18}O-potassium permanganate. The sulfonate ester, when treated with an aryl Grignard reagent, produced an optically active sulfone, whose configuration is known. It was found that ^{18}O-(-)-menthyl α-toluenesulfonate ester of the (R) configuration with p-tolylmagnesium bromide produced levorotatory ^{18}O-benzyl p-tolyl sulfone of the (S) configuration. Therefore, the Grignard reaction proceeded with inversion of configuration.

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26. Labeled potassium permanganate (90.2 atom %, ^{18}O) was obtained from Miles Laboratories, Inc., Elkhart, Indiana.

APPENDIX

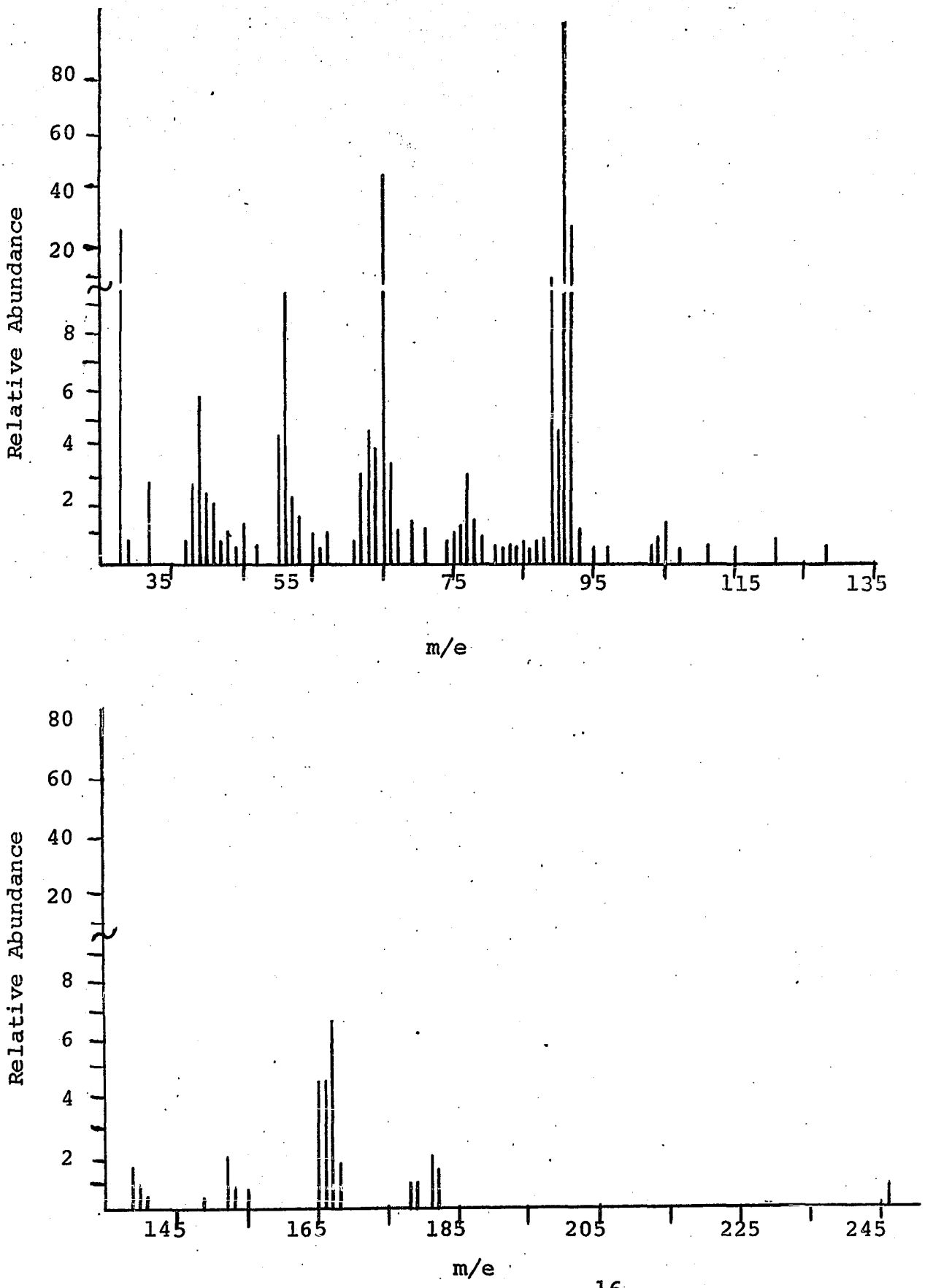

Figure A'. Mass Spectral Data for ^{16}O-Benzyl p-tolyl sulfone

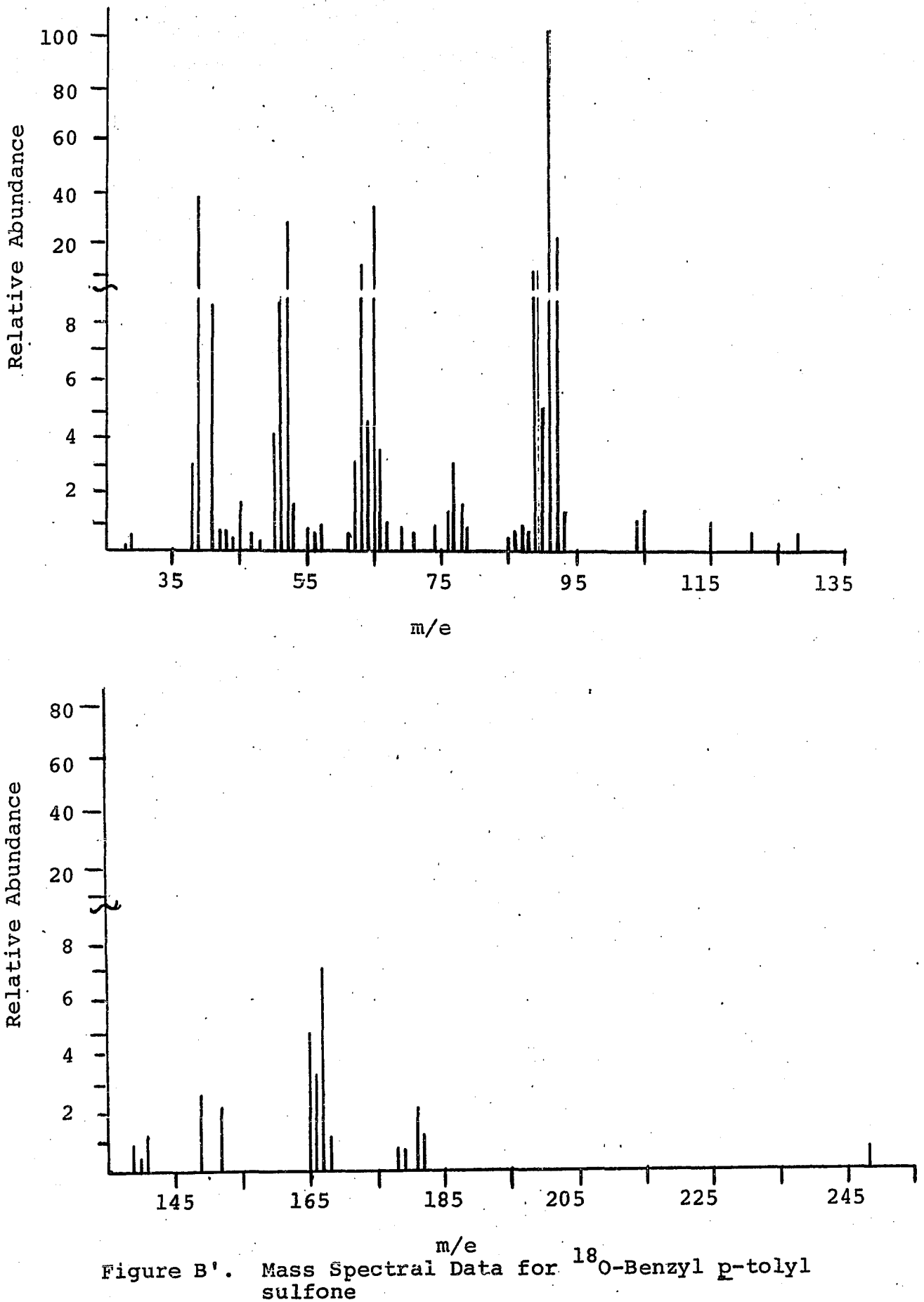

Figure B'. Mass Spectral Data for ^{18}O-Benzyl p-tolyl sulfone

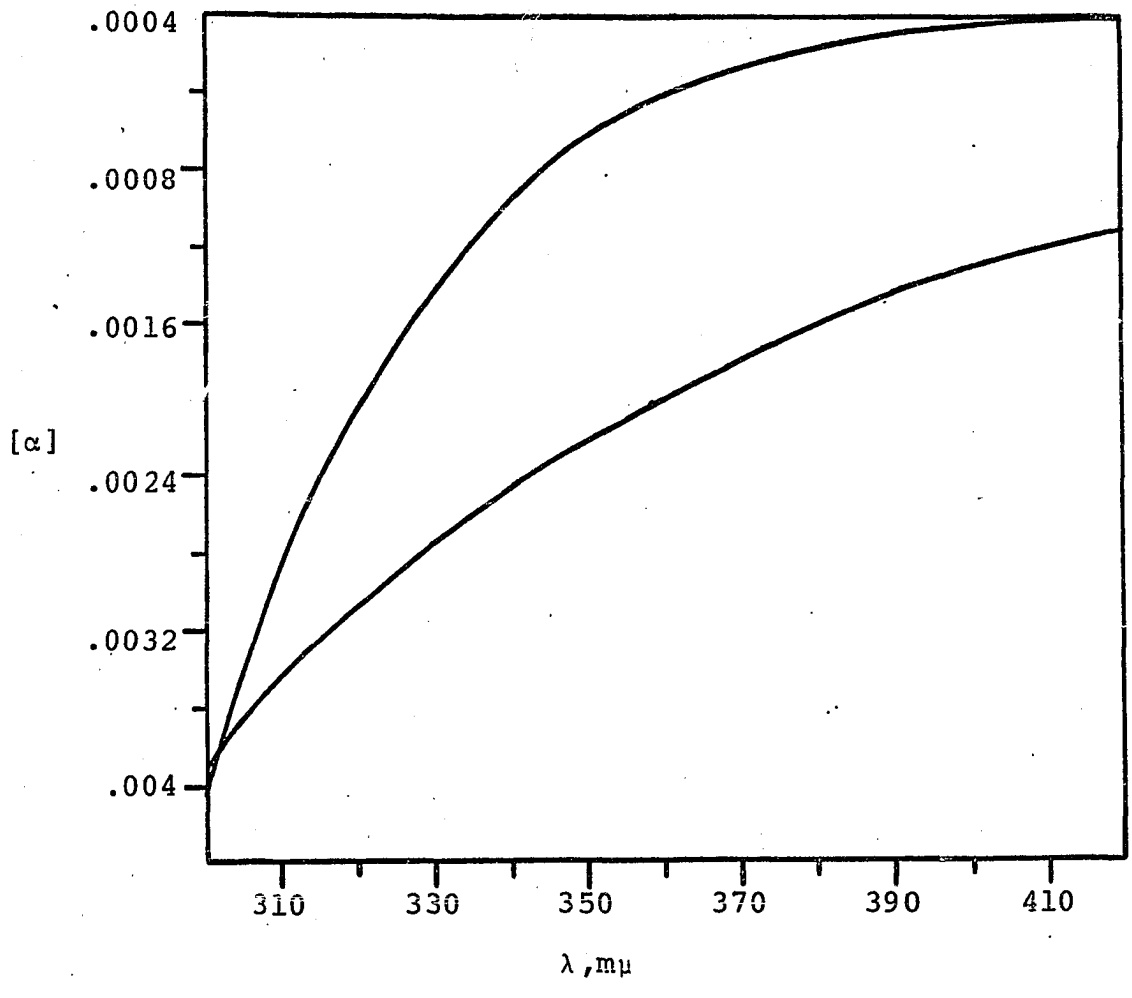

Figure C'. Optical Rotatory Dispersion Curves of (-)-Menthol and (-)-^{18}O-Benzyl p-tolyl Sulfone